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THE MICRO-ANATOMY OF NORMAL SKIN AS SEEN IN THICK SECTIONS.

K. V. SANDERSON,*
Institute of Dermatology, St. John's Hospital for Diseases of the Skin, London, W.C.2

AND

HELGA THIEDE,
Adelaide Children's Hospital, South Australia.

Some of the problems which are presented by skin tumours require for their olution a three dimensional view of the growth and its relation to normal tructures. This is particularly so in the case of those tumours believed to rise from the appendages of the skin. The purpose of this paper is to draw ttention to the thick section method of examining skin described by Leach 1952) and to compare its merits with those of other techniques which can be sed to investigate the architecture of skin tumours. Observations are recorded ere on the appearance of normal skin in these sections, which supplement hose given by Leach. The description of the skin tumours will be the subject of another communication.

Method.

A number of minor changes were made in the method which Leach outlined. Low viscosity nitrocellulose, recommended by him, was not available to us. Dry strips of " Mallinckrodt " Parlodion (celloidin) were used instead, and 2, 4 and 8% solutions n equal parts of absolute ethanol and ether were made up. To ensure gradual dehydration without excessive shrinkage, specimens were passed through 50, 70, 85, 95% and absolute ethanol in changes of 16 to 24 hours according to their size. Two changes of 24 hours each were given in equal parts of absolute ethanol and ether and the tissues were then soaked for 4 days each in 2 and 4% Parlodion solution ; 5 to 6 days were given in the 8% Parlodion solution and the containers were shaken occasionally to assist impregnation. To block out, fresh 8% Parlodion was poured into a glass container with a well fitting lid and the tissues arranged in it with the surface to be cut facing upwards. The lid was left on until all air bubbles had come to the

* Roussel Research Fellow, Institute of Dermatology.

surface and burst. When a rather firm skin had formed on the surface, the lid was lifted occasionally to ensure slow evaporation of the ether-alcohol. Finally, after approximately 4 days, the lid was left off completely to harden the Parlodion until the block " gave " very slightly.

Tissues were then cut out of the container, excess parlodion was trimmed off to form individual rectangular pieces which were mounted on dry wooden blocks with the aid of some 8% Parlodion. Ten to 15 minutes were usually sufficient to harden the joint. Blocks were stored in 70% ethanol in covered containers until required for cutting. Serial sections 500 μ thick were cut with a wedge shaped knife on a Leitz base sledge microtome No. 1300. Sections were cut dry, picked up with forceps, put down on clean cardboard and numbered with india ink. It was important to wait approximately one minute (usually until the next section was cut) for the india ink to dry slightly, otherwise it would run when the section was dropped into 70% ethanol. The sections were stored in 70% ethanol until required for staining.

Solutions used for staining were exactly as given by Leach.

(i) Five per cent aqueous aluminium sulphate A.R.
(ii) Stock anthracene blue solution.
Anthracene blue (C.I. 1062) G. T. Gurr, 0·5 g.
Five per cent aluminium sulphate, 100 ml.

Boil for 20 minutes. Allow to cool to room temperature. Filter next day.

Staining procedure employed :

(i) Two changes of distilled water, 15 minutes each.
(ii) Five per cent aluminium sulphate, 15 minutes.
(iii) Dilute anthracene blue, 48 hours.
Stock anthracene blue 1 part
Five per cent aluminium sulphate 20 parts } filtered after dilution.
(iv) Rinse in 5% aluminium sulphate, 1 minute.
(v) Wash in two changes of distilled water, 15 minutes each.
(vi) Wash in running tap water, 1 hour.
(vii) Two changes of 70% ethanol, 5 minutes each.
(viii) Two changes of 85% ethanol, 10 minutes each.
(ix) Two changes of 95% ethanol, 15 minutes each.
(x) Two changes of absolute ethanol, 15 minutes each.
(xi) Three changes of absolute ethanol and ether (equal parts), 10 minutes each.
(xii) Three changes of xylol, 10 minutes each.

Sections were then mounted in Canada balsam on clean glass slides. It was necessary to weight the coverslip until the balsam had begun to set to ensure that the mountant formed an even layer around the section.

To make sure that no mistakes occurred in the sequence of the serial sections when removing the Parlodion in stages (x) and (xi), they were taken through in batches of four or six in numerical order and mounted on previously labelled slides in the same order. As this procedure proved to be rather time consuming, some batches were taken through without removing the Parlodion. In this case absolute isopropyl alcohol was substituted for the absolute ethanol and ether-alcohol in stages (x) and (xi). Also, an attempt was made to use Gurr's DePeX as a mounting medium instead of Canada balsam, as it sets quicker and harder and is less likely to run. The result was not altogether satisfactory. Because of the thickness of the sections, the correspondingly thick layer of DePeX slightly changed the refractive index and the sections appeared to be insufficiently cleared. The use of DePeX was therefore abandoned and Canada balsam used for all the remaining specimens.

The thick sections were examined first of all with a stereoscopic microscope (Watson

nocular plate microscope) with magnifications of 12·5, 25 and 50, fitted with a glass age the underside of which has a matt surface. Illumination was by a high power ament lamp provided with a condensing lens and focussing adjustment (Cooke, roughton and Simms). For more detailed examination, a microscope with mono- ular objectives of 33 mm., 16 mm. and 8 mm. nominal focal length was used. Draw- gs were made by Miss A. Gretener from specimens examined with the stereoscopic icroscope. Photomicrographs were made with a monocular microscope fitted with Leitz photomicrograph attachment.

Material.—Twelve tumours which had been surgically removed were examined by is method. All the specimens were placed in neutral buffered formol saline imme- iately after excision. When the tissue had been fixed for several hours, a strip was ut from the centre of the specimen, across the smallest diameter, for histological xamination. The width of the strip varied from 0·3 to 1 cm., depending on the size nd nature of the specimen. The remaining two pieces of tissue were stored in 10% ormol-saline until they were embedded in celloidin. The tumours had been removed om the dorsum of the hand (6), neck (2), ear (1), scalp (1), nose (1) and lower part f the back (1). Each tumour was surrounded by a rim of skin, which in several nstances was 1 cm. or more in width. The observations which follow were made upon his skin. The patients were all living in South Australia.

Observations.

The Epidermis.—The stratum corneum is almost transparent except where t has become thickened, as at the edge of a senile keratosis, or where it is detached from the epidermis. The stratum granulosum cannot be distinguished s a separate layer. The stratum spinosum and stratum basale stain with moderate intensity and the main feature which distinguishes them from one nother is a fine band of pigmentation which is often seen in the region of the asal cells. Very little cellular detail can be seen with an 8 mm. objective, lthough melanocytes can sometimes be recognized in horizontal sections of he epidermo-dermal junction as small refractile bodies which are dispersed in regular pattern.

The contours of the surface of the epidermis and of the junction of the epidermis with dermis are visible except when the section has been cut truly vertically. They are best seen when the cut is oblique, and as the section can be examined from either side, both faces can be examined in such cuts. The linear furrows of the surface, which make a rhomboidal pattern, correspond to ridges on the under surface of the epidermis which are quite distinct from the nterpapillary ridges. The intersection of some of the deep linear ridges is pierced by one or more pilosebaceous follicles. The network of epidermal ridges has been described and illustrated by Leach and other workers, notably Horstmann (1952) and Hambrick and Blank (1954) who used split skin pre- parations, and therefore details will not be given here.

Mesodermal Structures.—The dermal papillae are dome shaped and are arranged in a regular fashion so that the distances between adjacent ones is uniform and less than their diameter. They vary in size from one region to another (cf. Leach's Figs. 2, 3 and 4). The pilosebaceous follicles and sweat

ducts are placed between the papillae. The epidermis forms a layer over these structures in the same way that a moulder's sand covers the surface of an embossed pattern. The appendages usually join the epidermis at the crest of a ridge, or where several ridges join together.

Arteries and veins can be seen clearly, but their terminal branches and capillary vessels cannot be distinguished in normal skin. In the same way only the larger nerves can be seen and these have characteristically undulating fibres. The meshwork of collagen fibres is relatively transparent but gives the effect of looking through lightly stippled glass. The pars papillaris of the dermis is almost transparent.

Fat cells of the panniculus adiposus have much the same appearance as in thin sections of paraffin embedded skin. The distribution of vessels and nerves can be followed very easily in this layer.

Pilosebaceous Follicles.—These are the most complex of the structures of normal skin to be seen in these preparations. Their frequency and form vary greatly from one area to another. Hair follicles at different stages of the cycle of growth can be seen. Some large follicles producing terminal hairs can be distinguished from others producing vellus hairs, but the distinction between these two types is not as easy to make as some previous writers have implied. There are features which are common to the follicles of all the areas examined and these will be dealt with before the regional differences are described. In the description which follows, the pilosebaceous unit is divided into three parts, the pilosebaceous duct, the sebaceous gland, and the hair follicle which comprises the hair bulb and root sheaths up to the point of attachment of the sebaceous gland.

As has already been mentioned, the pilosebaceous duct penetrates the pars papillaris of the dermis between the dermal papille. The outer aspect of the duct is smooth and of more or less uniform diameter until just before it joins the epidermis. The epidermal ridges, which run between the papillae surrounding the duct, converge on and join its outer part, giving the appearance of buttresses (Fig. 1). This is, of course, most evident where the ridges are deepest. It is this buttressing of the ducts which is largely responsible for the " collars " described by Leach in this situation. Pilosebaceous follicles tend to be grouped. Two, three or four follicles may open on the surface within a short distance of one another. Quite often the terminal part of the duct is a common opening for two or three follicles. The growth cycles of the individual follicles of a group appear to be quite independent of each other.

During the stages of the hair cycle the size of the hair follicle, the sebaceous gland, and the pilosebaceous duct change considerably. In general, the increase or decrease in size affects all these parts, but the follicles and glands show a greater range of variation than the ducts. (Figs. 1 and 6).

The Hair Follicle.—At its greatest length, in anagen, the follicle is two or

FIG. 1.—An active hair follicle with enlargement of the converging epidermal ridges to produced buttresses. The resting follicle to the left has no such buttresses. Contrast the pendulous sebaceous gland on the right side of the active follicle with the small buds mid-way down the resting follicle. Pinna, 500 μ section.

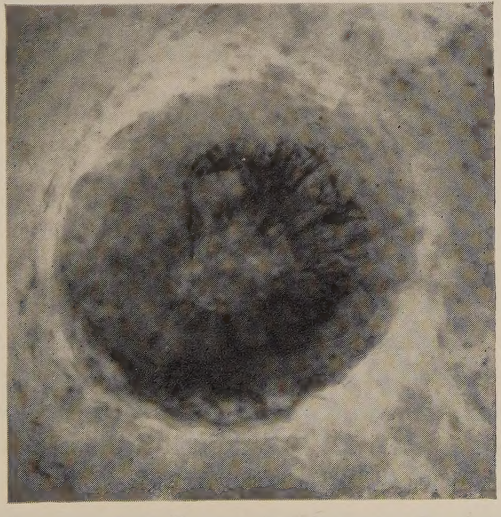

FIG. 2.—An active hair bulb and papilla seen from beneath. The dark dendritic cells are melanocytes lining the cavity of the bulb. Scalp, 500 μ section.

three times the length of the pilosebaceous duct. The hair bulb is a smooth terminal swelling which is hollowed to contain the hair papilla and from it arises the hair shaft which is surrounded by well developed root sheaths. Particularly in the skin of the scalp, dendritic melanocytes containing pigment are seen between the papilla and the hair matrix (Fig. 2). The density of pigmentation varies from one follicle to another, but in all it is confined to the dome

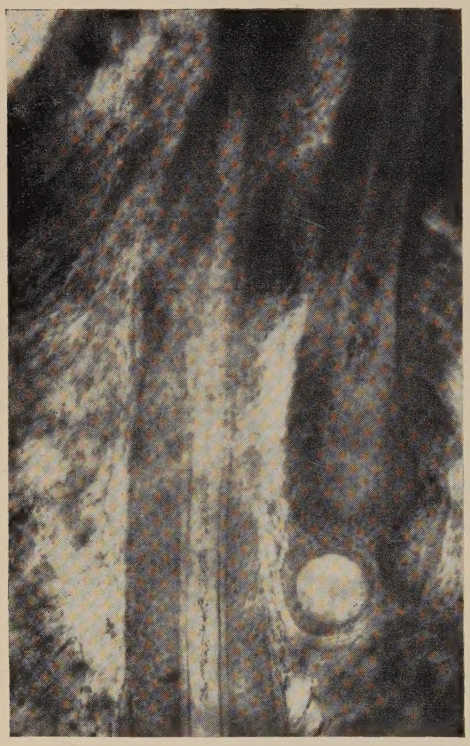

FIG. 3.—Two hair follicles of the scalp. On the left an active follicle, in which the connective tissue sheath and the root sheaths can be clearly seen. On the right is resting follicle showing the insertion of the club hair into the capsule. Immediately beneath this is a small keratinizing cyst. Scalp, 500 μ section.

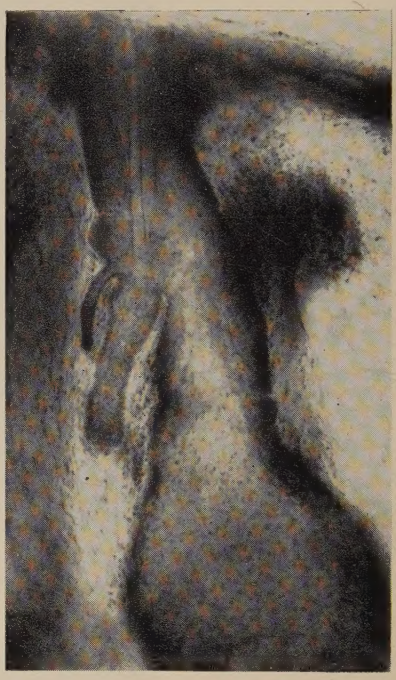

FIG. 4.—A resting hair follicle (probably in early anagen). A club hair is present. The relatively clear column of connective tissue beneath the follicle can be seen. Attached to it on the right is a large sebaceous gland, on the left side of the follicle a "collar", which connects with sebaceous gland behind the hair follicle. Pinna, 500 μ section.

of the papilla. A certain amount of detail can be seen in the root sheaths. The clear glycogen rich cells of the outer sheath are quite conspicuous and in some follicles the shape and alignment of the cells in the inner sheath can be discerned. The external surface of the outer sheath is smooth and more or less cylindrical in most follicles (Fig. 3). Minor irregularities are sometimes present. These are usually but not always associated with the point of attachment of the arrectores pilorum, which at this stage of the cycle is situated about

midway between the hair bulb and the junction of the follicle and sebaceous gland. The bulge (*Wulst*) of the external sheath, which Stöhr (1903) and Pinkus (1927) described as such a conspicuous feature of the developing foetal follicle, could not be found regularly in this or other phases of the growth cycle.

At its shortest, in telogen, the hair follicle has shrunk to a column considerably

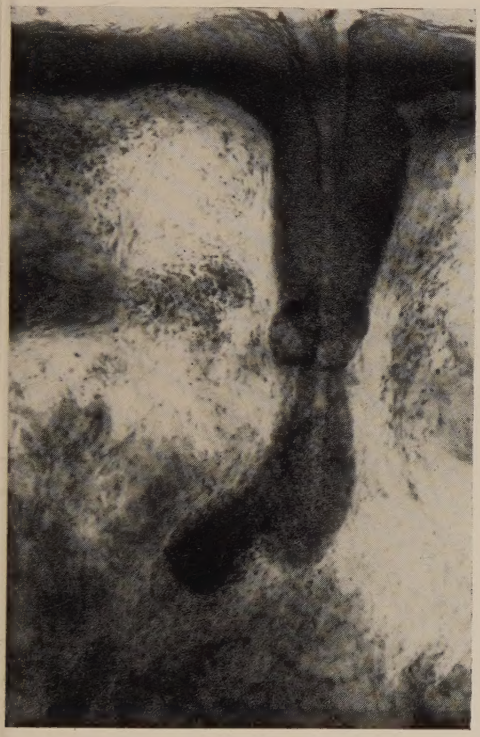

FIG. 5.—A resting follicle. The rudimentary follicle root makes an angle with the club hair and points down a column of loose connective tissue. The sebaceous gland is a rounded bud protruding from the wall of the follicle. Pinna, 500 μ section.

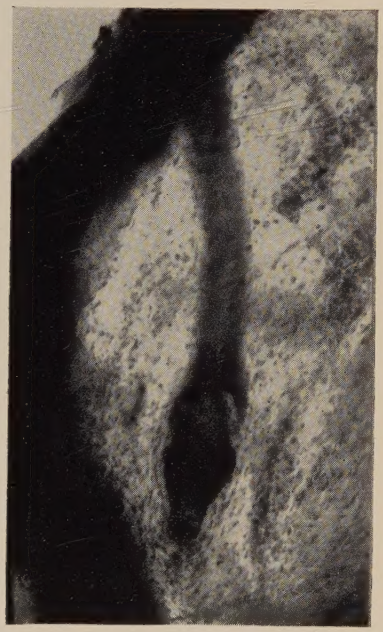

FIG. 6.—A very small follicle (cf. Fig. 3), showing a conical flange at the site of the sebaceous gland. No club hair is seen. Note the relative length of the pilosebaceous duct compared with the hair follicle. Scalp, 500 μ section.

less in length than its pilosebaceous duct. The club hair is anchored in an envelope of apparently undifferentiated cells. The diameter of this column diminishes beneath the base of the club hair, and it may be indented and slightly expanded at its termination by a nest of small, dark, closely-packed nuclei which are the cells of the resting papillae. There is no pigmentation of the resting follicle. Beneath some follicles in telogen there is a tract of connective tissue which is relatively transparent and rather more cellular than the surrounding connective tissue (Fig. 4). This tract may be straight and extend down

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to the level of the adjacent active follicles. In some places, however, it is curved or angulated relative to the resting follicle above (Fig. 5). Some follicles are so small that it would be easy to imagine that they are being newly formed (Fig. 6).

Most of the follicles are either in the active or resting phases. The transition from the former to the latter is seen very rarely and can be recognized by the

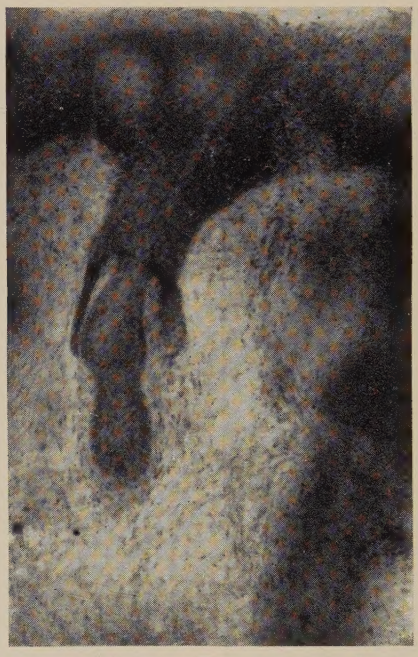

FIG. 7.—A resting follicle with a club hair. The sebaceous gland is rudimentary. On the left side it is collar two cells thick, on the right it is somewhat expanded but contains no mature sebum producing cells. The silhouette of an active follicle can be seen running obliquely down the right of the plate. Pinna, 500 μ section.

relative decrease in the length of the follicle, the loss of organization of its lower segment which is surrounded by refractile homogeneous connective tissue (the vitreous membrane), and by the presence of the club hair. The papilla is now a small collection of nuclei identical with that seen in telogen. Epithelial strands, such as Kligman (1959) described in the earlier stages of catagen, have not been seen. The majority of the follicles in an intermediate stage between full growth and resting seem to be in the earlier stages of anagen rather than in catagen.

Sebaceous Glands.—The sebaceous glands are less well developed in some regions, such as the trunk, dorsum of the hand and scalp, and here some hair follicles seem to be devoid of them. In other follicles they are represented merely by a thin conical flange or sleeve (Fig. 7). That this flange is in fact a rudiment

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of the sebaceous gland is demonstrated where a typical sebaceous lobule has developed from one part of it (Fig. 4). These flanges may partially or completely surround the upper part of the hair follicle and likewise so may the fully developed sebaceous glands. The picture of a more or less spherical sebaceous gland situated on the side of the follicle which makes an obtuse angle with the epidermis is a simplified version of what is seen on the trunk, but it is not at all what occurs on the scalp or face.

FIG. 8.—A pair of resting follicles superimposed. The arrector pili muscle is inserted into the connective tissue sheath of the nearer follicle. The follicle root has retracted to well above the point of insertion. Dorsum of trunk, 500 μ section. Drawing.

The Arrector Pili Muscle.—On the trunk, the muscle bundles of the arrectores pilorum are well developed and easily seen. They are attached to the connective tissue sheath at about the mid-point of the fully developed hair follicle and they are in close relationship to the sebaceous gland as they run obliquely upwards to terminate in the pars papillaris of the dermis. Their point of attachment remains unchanged in the perifollicular connective tissue during the different stages of the hair cycle. In telogen, the follicle may retract to a level above this point of attachment (Fig. 8). These muscles are also well developed on the back of the hand, but are less obvious on the scalp and in the skin of the nose in the specimens examined.

The regional differences in size of the hair follicle and hair shaft in the active

phase of the cycle are too well known to need further description. The usual histological sections, however, do not give an adequate idea of the great variation in the sebaceous glands. On the nose they are very numerous so that it may be difficult to distinguish the other structures in the dermis. Each unit comprises a perpendicular duct into which a number of bulbous glandular lobules discharge their secretion at different levels, looking somewhat like a small bunch of grapes. The hair follicle is a relatively insignificant structure and in the resting phase may join the duct at an angle. In the scalp the sebaceous glands are elongated and pendulous but small in relation to the size of the active follicle. They are usually unilobular and connect with the pilosebaceous duct by means of the conical flange.

There is a noticeable difference between the sebaceous glands on the two surfaces of the pinna. On the dorsal surface they are well developed and bulbous, usually multilobular and often encircling the hair follicle. On the ventral aspect they are poorly developed and generally unilobular. The vellus hair follicles on the two surfaces do not show a great degree of difference. The line of separation of these two surfaces runs along the helix, a little posterior to the tip of the cartilage.

Eccrine Sweat Apparatus.—The sweat gland and coiled part of the duct lie in the deeper part of the dermis or in the subcutaneous fat just beneath it. The ducts take a straight or slightly sinuous course to the surface. Neighbouring ducts, however, may reach the surface in quite different directions. The duct has a funnel-like expansion as it reaches the epidermis, which it may enter at one of the interpapillary crests. There are no " buttresses " for the sweat ducts. No apocrine glands were found in any of these sections.

Several minor abnormalities of the adnexal structures should be recorded. We have confirmed Leach's observation that a number of sweat ducts do not reach the surface, but end in blind spherical dilatations. This feature is seen occasionally in normal skin but is much more frequent below epithelial tumours. This suggests that the change occurs when the terminal part of the sweat duct has been destroyed. In several other sweat ducts there are segments of saccular or sausage-shaped dilatations which appear to be made up of a series of pouches rather than an even and regular expansion of the lumen.

Sqamous metaplasia of a sebaceous gland is not uncommon, producing a keratinized cyst attached to the pilosebaceous duct. On the trunk, several of these cysts contain hair shafts coiled up within them and the pilosebaceous duct is filled with a keratinous plug (Fig. 9). A number of small keratinizing cysts have also been seen in relation to hair follicles on the scalp. They are found adjacent and possibly connected to inactive follicles (Fig. 3). They may be the horny pearls which Pinkus (1927) described as occurring in the lower part of the hair follicle when this is reduced to an epithelial strand in the phase of catagen.

The appearance of the connective tissue is considerably modified by two

processes. Simple inflammation produces a cellular exudate from the smaller vessels which outlines their course. At the same time, the presence of cells obscures the details of adjacent structures if the infiltrate is at all dense. In elastoid degeneration of the collagen, which occurs in skin exposed to excessive amounts of radiant energy, the upper part of the dermis becomes clouded. The regular interlacing of collagen bundles, and indeed many of the structures embedded in the dermis are obscured by this change. The inflammatory and degenerative processes just mentioned are usually found in skin taken from the exposed areas of middle-aged and elderly Australians.

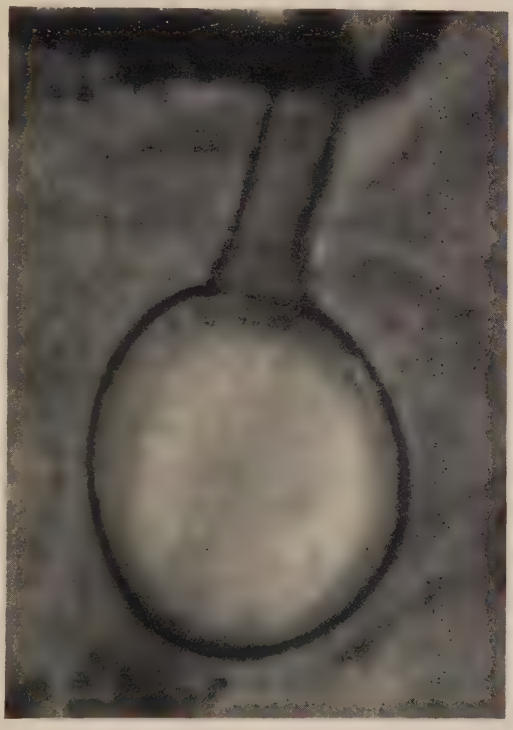

FIG. 9.—A milium, showing the cystic dilatation of the sebaceous gland, which has squamous epithelium. The duct leads from the apex of the cyst and is plugged. A hair shaft is coiled up within the cyst. The faint outline of the follicle root can be seen. It is behind the lower pole of the cyst a little to the left. Dorsum of trunk, 500 μ section.

DISCUSSION.

The observations have been made upon the normal skin around a series of tumours removed from a limited number of regions of the skin surface. They are presented primarily to provide the background for a later communication in which the architecture of tumours will be described. A number of important regions of the skin are not represented in our specimens. Within these limitations our findings agree largely with those of Horstmann (1952). Hambrick and

Blank (1954), Van Scott and MacCardle (1956) and Montagna and Van Scott (1958) to mention some of the more recent studies on the micro-anatomy of the skin, and with the description of the human hair cycle by Kligman (1959).

The convergence of interpapillary epidermal ridges upon adnexal ducts has been described by Horstmann (1952) as the rosette pattern. He does not mention the enlargement of these ridges around the pilosebaceous ducts to form buttresses. Indeed, in normal skin this enlargement is not very pronounced and its degree is related to the depth of the interpapillary ridges. The buttresses cannot be seen in the thin sections usually employed in histology. Their presence can be inferred, however, from changes that take place in seborrhoeic warts and cellular naevi. Large buttresses have been demonstrated in split specimens of seborrhoeic warts and verrucous cellular naevi (Sanderson, unpublished data).

Pinkus (1958) has suggested that the pilosebaceous duct forms a unit which extends to the skin surface and that this, together with the intraepidermal part of the sweat duct acts in a different way from the epidermis in senile keratoses. It would be interesting to determine whether the buttresses follow the epidermis or the duct in their reactions.

The conical flange or collar by which many sebaceous glands are attached to the follicle was described by Zimmermann (1935). He showed that it was a conspicuous feature in horizontal sections of the vellus hair follicle cut through this region. In these it is seen as an annulus two or three cells thick, completely encircling the follicle. He also showed that the collar was by no means always regular, but might have outgrowths towards the epidermis, or laterally out into the connective tissue. He regarded the structures as the sebaceous gland anlagen. We have found these collars on terminal hair follicles of the scalp. The variation in the form of the follicles suggests that the collars are not merely the anlagen of sebaceous glands and that not all sebaceous glands arise from such collars. They seem also to be the resting phase of the sebaceous gland, which may or may not coincide with the resting phase of hair growth. The acute angle between the collar and the hair follicle is often filled by connective tissue having a higher acid mucopolysaccharide content than that of the rest of the connective tissue sheath (Sanderson, 1959).

A structure analogous to the blind bulbous ending of sweat ducts in the dermis has been produced experimentally by Lobitz, Holyoke and Brophy (1956). They made a horizontal cut in normal skin with a fine knife, transecting sweat ducts in the mid-dermis and followed the stages of regeneration by serial biopsy. They found that the distal segment of the duct became atrophic, while the proximal segment proliferated and if it failed to reach the surface produced a blind sac. Within this there were spiral partitions having a likeness to the spirals of the intraepidermal sweat duct. We have not been able to examine the interior of the dilated duct ending in our thick sections, but similar formations

we have seen in thin sections, have consisted simply of a duct leading to a thin walled sac whose contents are amorphous debris. The cause of the segmental dilation seen in a few ducts is obscure. It would be too easy to assume that these are due to poral obstruction, and it is just as likely that they represent metaplasia of the duct epithelium. They do not correspond, either in situation or form, to the ampulla described by Loewenthal (1960).

A milium or epidermal cyst results when a sebaceous gland undergoes squamous metaplasia and becomes distended by accumulated keratin. This has happened in the example which is illustrated and in addition the pilosebaceous duct is plugged and the hair shaft is coiled up within the cyst. The mechanism by which this occurs is obscure. It is most likely that past damage to the sebaceous gland is the primary cause of the metaplasia. Blockage of the duct follows and the hair only finds its way into the cyst when this has grown to such an extent that the duct of the sebaceous gland is dilated and patulous. The normal sebaceous duct is narrow and makes an acute angle with the hair shaft as it joins the follicle. Haber (1953) described this sequence of events in the pathogenesis of milia some years ago.

Our observations have convinced us that thick sections give a better overall picture of the micro-anatomy of the skin and of certain tumours than any other method. Where cytological study is essential, a reconstructive technique from serial thin sections such as that employed by Van Scott and MacCardle, has obvious advantages. The final model, however, is a rather crude approximation to the actual structure and is divorced from its surroundings. The added drawback of the considerable time and labour involved in producing a model of a small piece of tissue restricts the value of this method for systematic investigation of tumours. We attempted to cut alternate thick and thin sections from our celloidin blocks, but found that it was impossible to get satisfactory thin sections. However, paraffin embedded sections of the central part of the specimen provide a satisfactory picture of the cytology of the tumour. We have found it impossible to visualize any but the simplest changes in form from the direct examination of serial thin sections and the frequent description of the interpapillary ridges as rete pegs, cited by Leach, is an example of the fallacies of this method.

Splitting the skin at the epidermo-dermal junction gives an unrivalled view of the contours of the epidermis and the terminal parts of the adnexae. The surface of the dermis can be examined after light nuclear staining and the two faces correlated. However, the main part of the adnexae is often retained in the connective tissue and cannot be seen. This method is of value in examining some superficial tumours, such as seborrhoeic warts and superficial basal-cell carcinomata but is useless where invasion of the dermis by the tumour has occurred.

The examination of thick sections, as Leach pointed out, requires care and

straining the eye to the limit of its resolving power. The picture shown by these preparations is so different from the flat brightly coloured sections one is accustomed to, that it takes time to become orientated and to discern the relationships and true form of the various structures. However, a surprising amount of fine detail can be seen, as the illustrations of this paper show.

Summary.

Twelve surgical specimens of skin tumours have been cut in sections 500 μ thick, stained by the method of Leach and examined with a stereoscopic microscope.

The appearance of the skin surrounding the tumours is described. The epidermis and its appendages can be seen in three dimensions. There is great variation in the size and form of the pilosebaceous follicles from one place to another and at various phases of the hair cycle. Many follicles show two features which have received little attention in the past, the convergence of buttress-like epidermal ridges on the pilosebaceous duct and the presence of a conical flange or collar which is the rudiment or resting phase of the sebaceous gland.

The formation of milia by squamous metaplasia and cystic dilatation of sebaceous glands is illustrated and the presence of some sweat ducts which end in blind dilated sacs within the dermis is mentioned.

The observations are in general agreement with previously published reports of the micro-anatomical features of the skin. The merits of the various methods used for such investigation are discussed with particular reference to displaying the micro-anatomy of epidermal tumours.

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HUMAN ELASTIC FIBRES.

Electron Microscopic Appearances of the Elastic Fibres of Human Skin in Thin Section.

ARWYN CHARLES, M.Sc., Ph.D.

Departments of Dermatology and Biomolecular Structure, The University, Leeds.

The first electron microscopic examination of thin-sectioned elastic fibres appears to be that of Bahr and Engström (1954). The fibres shown by them in cross section were homogeneous, except for a more electron-dense boundary. Linden *et al.* (1955) examined sections of human skin and showed spirally twisted fibrils which they considered to be elastic tissue.

Rhodin and Dalhamn (1955), so far as I am aware, have published photographs of the only technically adequate sections of elastic tissue. In their material, the lamina propria of rat tracheal mucosa, the elastin showed no well defined structural characteristics, but there was clear evidence that it was fibrillar. These authors concurred with the previously expressed opinion of Hall *et al.* (1955) that the elastic fibre consisted of at least two components, an inner fibrillar component about 70 Å thick, embedded in an amorphous cementing material. More recently, Saxl and Hall (private communication) suggested that the inner component might contain aggregates of lipoprotein (see also Lansing *et al.*, 1955) and consequently might appear as an electron-dense material in osmium stained tissue.

The present paper describes representative appearances of the elastic tissue in a variety of normal and pathological skin biopsy specimens. The elastic fibres illustrated are probably best regarded as normal, because although certain of the lesions chosen involve changes in the dermal fibrous tissue, these changes generally are of quantity, rather than of character. In diseases where the dermal tissue is grossly affected it appears, electron microscopically, to form a poorly differentiated mass within which elastic fibres cannot be distinguished from the collagen.

Investigation.

Biopsy specimens were taken from normal skin adjacent to a spider naevus near the left eye of a 45-year-old woman (used to illustrate Fig. 1A, B, E, and F) from the knee of a 16-year-old boy suffering from Miescher's elastoma (Fig. 1I), from the back of another boy aged 11 years, suffering from the Ehlers Danlos syndrome (Fig. 1H), from normal skin of the scalp above the left ear of a 48-year-old man (Fig. 1C and D) and from uninvolved skin on the wrist of a 77-year-old man suffering

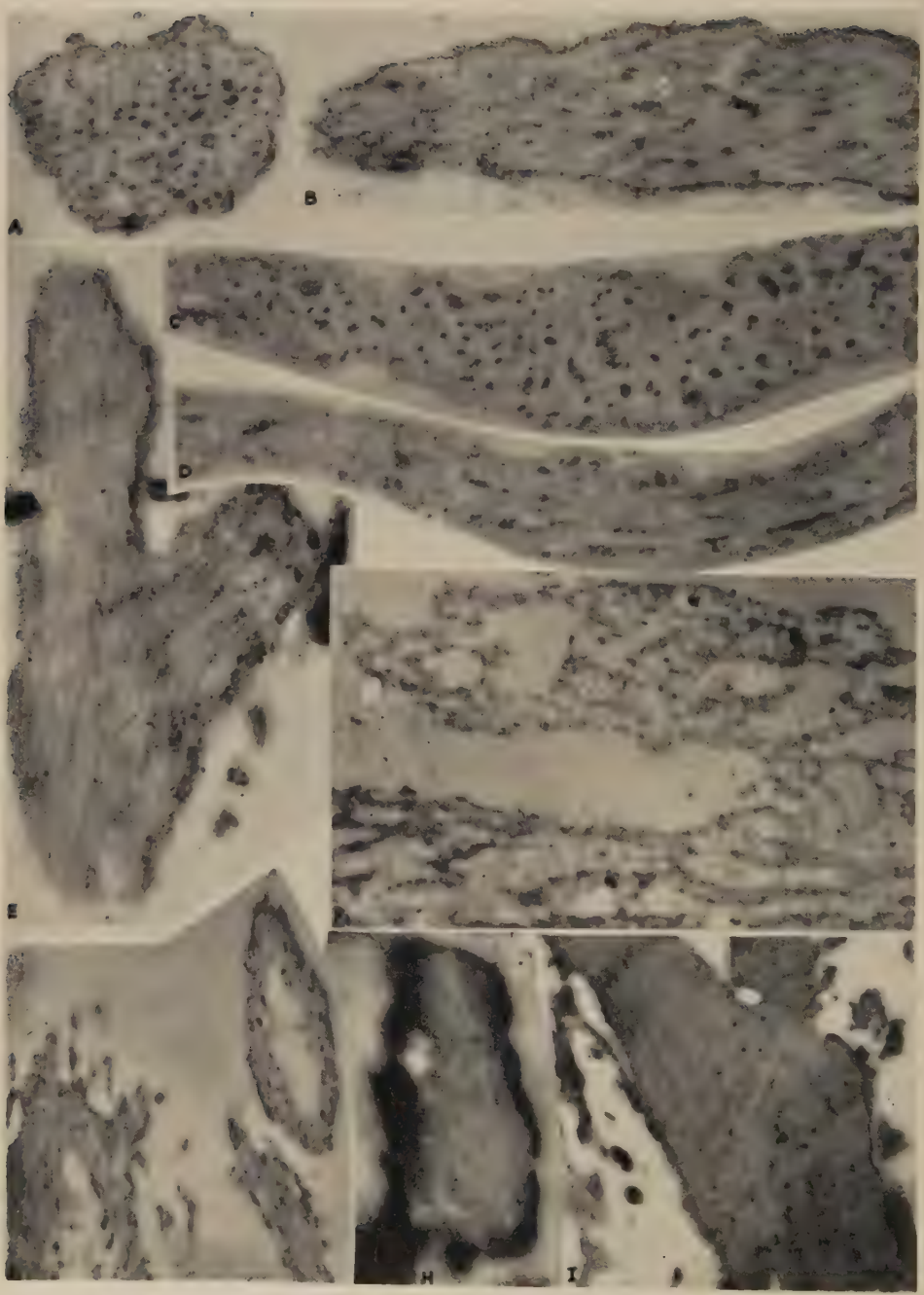

FIG. 1.—The magnifications are : A and B, ×31,500 ; C and D, ×12,000 ; E, ×20,000 ; F, ×13,500; G, ×8500 ; H, ×27,000 ; I, ×12,500.

from constitutional eczema (Fig. 1G). Before incision, the skin was anaesthetized with 2% procaine containing 1 : 40,000 w/v adrenalin. The subsequent fixation and dehydrating techniques and the final embedding of the material in monomeric *n*-butyl methacrylate at 45° C. were in accordance with usual practices (see Charles and Smiddy, 1957). Sections were examined in a Metropolitan Vickers E.M.3 electron microscope.

Results and Discussion.

Normal elastic fibres are readily distinguishable from the collagen of dermal tissue : with the phase contrast microscope they are seen as smooth, shiny, black fibres among the lighter collagen ; in the electron microscope the cross striations of the collagen fibrils allow easy differentiation from the elastin. The typical appearance of elastin in cross section and in slightly oblique longitudinal section is shown in Fig. 1A and B. Both these fibres occurred adjacent to each other on the same electron micrograph. Each are seen to have an electron-dense, membranous, outer sheath and tend to be of somewhat irregular outline. Enclosed within the sheath is a less dense uniform matrix embedded in which are dense elements, the fibrillar nature of which is best suggested in Fig. 1E. This shows the elastin cut at a point of branching, and the fibrillae, measuring 200 to 500 Å thick, have a beaded appearance. Such measurements, however. are of dubious value and large variations in diameter, between 200 and 2500 Å, can be seen in the cross section shown in Fig. 1C, which fibre occurred on the same micrograph adjacent to that of Fig. 1D. In both, the outer sheath is vestigial or absent. This is true also in the fibres of Fig. 1G, which are hollow and of somewhat ragged outline ; the dense fibrillae here are about 200 to 500 Å diameter.

In Fig. 1F the outer membrane of the branching fibre is absent, and the lighter matrix seems to have been leached away leaving a fine, granular deposit. The fibre outline is broken and the dense fibrillae reach diameters of about 1500 Å. Such elastin is seen not uncommonly, but its significance is not known. In the more massive elastic fibres shown in Fig. 1I, the dense fibrillae are somewhat faintly shown and it seems to be that as the elastic fibres increase in size, the denser material disappears. This may explain the homogeneous appearance in cross section of the elastic fibres of Bahr and Engström. In Fig. 1H we see, on the left-hand surface of the sectioned fibre, some slight suggestion of the fine 70 Å fibrillae of Rhodin and Dalhamn. Such an appearance is unusual and was seen better in the original electron micrograph than in this photograph. Examination of the original plate suggests that the fibrillae are derived from the ground substance outside the elastic fibre, but have become entangled on to its surface.

Thus although there is ample evidence to support the commonly held view that the elastic fibre is a two component system of matrix and embedded fibrillae, the form, at least, of the latter is variable. Such variability, together

with the electron-dense nature of the material, is consistent with the fibrillae being deposits or accretions of a lipoid substance.

Summary

Electron micrographs are shown to illustrate the appearances of elastic fibres in human skin. The fibres consist of a lighter material in which irregular strands or accretions of a denser material are generally embedded. These seem to become fainter in the thicker elastic fibres, which consequently are more homogeneous in appearance.

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DISTRIBUTION OF PUBIC HAIR IN A SAMPLE OF FIT MEN.

DONALD McGREGOR, M.A., M.R.C.S., L.R.C.P.

General Practitioner, Bonar Bridge, Sutherland.

It has been commonly observed that pubic hair in males covers an area of the body consisting typically of the skin over the horizontal rami of the pubes around the sides of the attachment of the scrotum, and a variable area of the lower abdominal wall (Fig. 1a). This last area is frequently triangular with its base on the pubes and its apex at the umbilicus, but it may be reduced to a narrow band running up the midline to the umbilicus from the symphysis. It has also been commonly observed that in females the distribution of the pubic hair is different, the abdomen being free from hair, while the upper margin of the hair covered area is a distinct curved line, concave upwards, joining the lower ends of the furrows marking the position of the inguinal ligaments (Fig. 1b). This so-called female-type distribution is said to occur in males also in conditions of submasculinity which accompany such an endocrine disorder as Fröhlich's syndrome. Similarly, the so-called male-type distribution is found in women with disorders of the adrenal cortex.

Dupertuis *et al.* (1945) examined photographs of 964 male college students with an average age of 18 years, and 96 clinical subjects ranging in age from 30 to 40 years. This sample of 1060 men was not unselected, more particularly in respect of the heavy preponderance of young men. The present count, carried out at about the same time as the American one and in ignorance of it, records a larger sample and uses a somewhat different scheme of classification, but arrives at not wholly dissimilar conslusions.

Investigation.

The sample of men examined consisted of 3,853 British Army "other ranks" travelling by sea in a certain ship during one year, November 1943 to November 1944. All the B.O.Rs. travelling in this ship during this time, save for a small number of miscellaneous hospital cases, were included in the sample. Apart from trivial maladies such as scabies, pediculosis and tinea cruris they were all fit men, but in view of the fact that the British Army overseas at that date can be presumed to have had all cases of frank endocrine disorder, and almost all males over 45 years of age, eliminated from it, the sample cannot be regarded as strictly unselected. Examples of "female" hair distribution which have hitherto been noticed to be associated with endocrine disorder would not appear in it, and any change of hair pattern with age would not be fully represented.

Two observers made the count, each of them counting and classifying approximately half the sample. Practical difficulties unfortunately precluded the counting and classifying of the whole sample independently by each observer. The men filed past the observers naked in two files, and on most occasions when counts were being made, the observers had no responsibilities for routine medical inspection and could give their whole attention to the observations. Men showing the "male" type of

distribution were described as Group I ; men showing the " female " type of distribution were described as Group II. On the very first occasion on which observations were made (see Table I, Count I) both observers noted independently that a substantial number of men had their pubic hair disposed in a way which was neither characteristically " female " nor characteristically " male " and it was impossible to include them without doing violence to the categorical descriptions in either Group I or Group II. The appearance of the pubic hair in this extraordinary class of subject is shown in Fig. 1c and the points to be noted about it are that the hair does not extend, as it does in Group I, to any degree whatever on to the abdomen even as a thin vertical line. On the contrary, it is closely and thickly gathered round the base

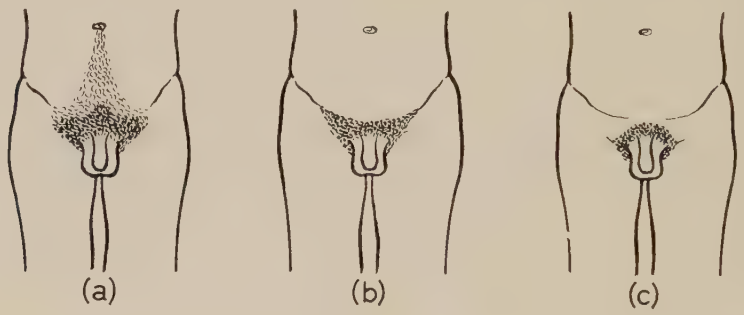

Fig. 1.

of the scrotum with sharply defined margins, and does not extend as it does in Group II laterally in gradually thinning extensions along the lower inch or so of the inguinal furrow. Moreover, while the upper margin of the pubic hair in Group II is gently concave upwards, the upper margin in this third type is convex upwards. It was immediately decided to include these types in a separate Group III.

The classification of individuals into these three groups, while easy in the most strongly marked types, was not without doubt in all cases, especially at the beginning of the investigation. And both observers were aware of the importance of reaching unanimity as to the way they proposed to classify doubtful examples. Frequent consultations therefore took place over individuals, and both observers from time to time surreptitiously noted the other's method of classification. After a few counts, both observers were satisfied that the men they were examining did in fact manifest three discontinuous variations in the distribution of their pubic hair and that each was recognizing and describing similar distributions as being members of the same groups.

Results.

The investigation had now become an attempt to discover the proportions in the fit male population of three types of pubic hair distribution. Table I summarizes the counts made on ten batches of men, 3,858 in all. It will be seen that the percentage of Group I varies in different batches between 72·1% and 90·8%, the mean percentage being 85·2% with a standard deviation of 5·35%. The percentage of Group II varies in different batches between 2·97% and 8·8%, the mean percentage being 4·65% with a standard deviation of 2·52%. The percentage of Group III varies in different batches between 6·27% and 19·1%, the mean percentage being 10·20% with a standard deviation of 4·10%.

It should be noted that the highest deviation from the mean percentage in all three groups was obtained in Count I. This may be explained by the observers not having entirely made up their minds how the three types were to be classified.

TABLE I.—*Distribution by Groups.*

	Group I		Group II		Group III		Total	
Count	No.	%	No.	%	No.	%	No.	%
I	294	72·1	36	8·8	78	19·1	408	100
II	547	80.1	41	6·0	95	13·9	683	100
III	86	87·8	4	4·08	8	8·16	98	100
IV	757	82·4	32	3·5	126	14·67	915	100
V	270	89.2	12	3.96	21	6·93	303	100
VI	120	88·2	7	5·14	9	6·62	136	100
VII	345	85·35	16	3·97	43	10·76	404	100
VIII	137	89·0	6	3·9	11	7·1	154	100
IX	304	90·8	10	2·97	21	6·27	335	100
X	367	87·0	19	4·5	36	8·54	422	100
Total	3227		183		448		3858	
Mean %		85·2		4·65		10·20		
S.D.		5·35		2·52		4·10		

Studies on the development of pubic hair (Priesel and Wagner, 1930; Greulich, 1942), have shown that there is absence of pubic hair from the abdominal wall of both boys and girls at puberty. It seemed possible therefore that the restricted distribution of pubic hair classified here as Group III might be an immature form. Counts IV and V in Table I bear this out.

On this occasion, 1218 men were divided into two groups, 915 of them being under 30 (Count IV) and 303 of them being over 30 years of age (Count V). In Count IV (under 30's) the frequency of Group III is markedly high, and that of Groups I and II is low. In Count V (over 30's) the frequency of Group III is low and that of Group I is high. No decided effect on the percentage of Group II is noticeable, but this is not surprising in view of the small number of men in the count. The observers were inclined to the view that Group III is an immature form of distribution which tends to develop into typical Group I and possibly typical Group II, though the age at which it does so varies from individual to individual. In view of this interesting finding, the observers desired to separate all later batches into those aged under 30 and those aged over 30. There were practical difficulties in arranging for this, and the idea had to be given up.

DISCUSSION.

Dupertuis *et al.* described three types of pubic hair pattern all of which were characterized by hair on the abdominal wall. In their count of 964 men of about 18 years of age, these three groups, corresponding to Group I in the present counts, accounted for 61·7%, a figure lower than would be accounted for by chance and due no doubt to the sample being strictly selected by age.

Among their 96 men aged 30 to 40, however, their Group I examples numbered 83·3%, within, that is to say, the standard deviation for Group I recorded in this paper. Dupertuis *et al.* did not recognize the pubic hair distribution described here as Group III, regarding it as indistinguishable from what they describe as the " horizontal " or female type. They found this horizontal type in 38·3% of their 18-year-olds and in 16·7% of the 30 to 40 age group, the latter figure corresponding very well with the percentages for Group II and III combined for the total of the present counts. Absence of correspondence between this figure of 16·7% and the percentage of Groups II and III in Count V (10·8%) is due to the small numbers considered—96 in the American case, 303 in the present case.

The evidence of these counts supports the conclusion of the American workers that what has often been described, on the testimony of clinical material, as a feminine or female type of distribution occurs in a substantial number of normal males, who do not show other feminine characteristics. It would be altogether preferable to abandon the description of pubic hair patterns by the words " male type " and " female type ".

It appears from these and the American counts that the final pattern of pubic hair distribution is only gradually acquired, and does not reach its final form till after the age of thirty.

Summary.

An investigation is described to establish the proportions in which pubic hair occurs in a sample of fit males in the form hitherto described as " male " and " female ".

A third type was discovered sharply distinguishable in its most pronounced form from both the other types. Two observers performed the counts on a sample of 3,858 men. The mean percentages of the three types were found to be:

Type I (" male ")	85·2% : S.D. 5·35%.
Type II (" female ")	4·65% : S.D. 2·52%.
Type III	10·20% : S.D. 4·10%.

The suggestion is made that Type III is an immature form of Type I, and possibly also of Type II, and the opinion is given that the terms " male " and " female " distribution of hair are misleading.

The writer is deeply indebted to Hamish Allan, Esq., M.B., for making available the facilities required for this investigation, for acting as an observer himself, and for taking a warm-hearted interest in the whole matter.

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FAILURE OF PROGESTERONE TO ENLARGE SEBACEOUS GLANDS IN THE FEMALE RAT.

F. J. EBLING.

Department of Zoology, Sheffield University.

THERE have been conflicting reports on the effects of progesterone on sebaceous glands. On the one hand, Haskin, Lasher and Rothman (1953) and Lasher, Lorincz and Rothman (1954) have stated that its stimulatory action on the sebaceous glands of spayed adult rats is comparable with that of testosterone. Zeligman and Hubener (1957) have claimed that it produces mild to moderate acne in women, involving slight but not statistically significant enlargement of the sebaceous glands. On the other hand, Ebling (1948) found no evidence that the sebaceous glands of intact immature rats were affected by progesterone (1 mg. daily for 20 days) even though they were markedly enlarged by a similar dose of testosterone. These findings are in line with those of Jarrett (1959) who showed that whereas testosterone both increases sebum production and aggravates the lesions of acne vulgaris in man, progesterone has neither of these effects.

The contradiction between the results of Haskin *et al.* (1953) and those of Ebling (1948) might have one of several explanations. First, Ebling used intact rats and Haskin *et al.* used spayed ones ; it is possible that the effects of progesterone can be prevented or offset by the presence of the ovaries, since it is well established that oestrogens reduce the size of the sebaceous glands (Ebling, 1948, 1954, 1955). Secondly, the responses of immature rats as used by Ebling may not be the same as those of adult rats as used by Haskin *et al.* The sebaceous gland may resemble the mammary in that it only responds to progesterone after priming with oestrogen. The experiments reported here were designed to investigate these hypotheses.

INVESTIGATION.

For each of three separate experiments, a series of litters from a random mated colony of albino rats was used. Each experimental group contained one rat from each litter. In the first experiment, intact rats aged 5 weeks were treated for 3 weeks with progesterone, and one group received oestradiol for the first 11 days of this treatment. In the second experiment, spayed rats aged 5 weeks were treated for 3 weeks with progesterone, or with progesterone and oestradiol. In the third experiment, both intact and spayed rats aged 19 weeks were treated for 3 weeks with progesterone.

Cylinders of progesterone (about 8 mg. in weight) and 1 : 9 oestradiol cholesterol (about 5 mg. in weight), both from Organon Laboratories Ltd., were implanted under the skin of the back. The implants were weighed before and after use.

All the rats were injected intraperitoneally with 0·1 mg. of colchicine in water per 100 g. body weight at 10 a.m. and were killed 5 hours later, as described previously (Ebling, 1954).

The whole skins were removed by a mid-dorsal incision, wetted with alcohol, fastened to cork boards and fixed in Bouin's solution for 24 hours. After washing in water for 24 hours, the mammary glands were dissected off and prepared as whole mounts after staining in Ehrlich's haematoxylin.

Samples of skin taken from near the midline in the anterior dorsal region were embedded in ester wax (Steedman, 1947), sectioned sagitally at 7μ and stained in Ehrlich's haematoxylin and alcoholic eosin. For each rat, the number of sebaceous cell nuclei was counted in a total of 25 gland sections, taken consecutively in two or three slides chosen at random. The result is shown expressed as the average number of nuclei per gland section. Arrested mitoses were counted for 50 such gland sections. From these figures it is possible to make comparative calculations of the cell life or "turnover time" (Leblond and Walker, 1956; Ebling, 1957*a*). In one experiment only, the outlines of the 25 gland sections were traced by means of a camera lucida and their areas determined by means of a planimeter. This makes it possible to estimate gland volume, cell size and the number of cells produced in each gland per day by methods of calculation which have been described elsewhere (Ebling, 1957*a*).

Results.

Sebaceous Glands.

In intact rats aged 8 weeks at death (Table I), progesterone implanted for 21 days had no effect on gland size, cell production or turnover time. Concomitant treatment with oestradiol for the first 11 days did not affect the results.

Table I.—*Sebaceous Glands of Intact Rats at Eight Weeks of Age.*

	Groups.		
	Intact controls.	Progesterone (21 days).	Progesterone (21 days). Oestradiol (11 days).
Average daily absorption of progesterone	—	0·15 mg.	0·18 mg.
Average daily absorption of oestradiol	—	—	3·5 μg.
Nuclei per gland section	10·1±0·39	11·0±0·52	9·6±0·39
Mitoses per 50 gland sections in 5 hours	13·5±1·81	13·4±1·30	13·9±1·62
Turnover time (days)	9·5±1·66	9·8±1·72	9·1±1·48

Means and standard errors are for groups of 10 rats.

In rats aged 8 weeks at death, which had been spayed 21 days previously (Table II), implantation of progesterone for 19–21 days had no significant effect on gland volume, and there were no significant changes in cell size, cell production or turnover time. Concomitant implantation of oestradiol for the whole 19–21 days during which the rats were treated with progesterone, caused a significant reduction in gland volume. This appears to be accounted for in large part by a decrease in turnover time, but the rate of cell production was probably also decreased.

TABLE II.—*Sebaceous Glands in Rats Spayed Nineteen to Twenty-one Days Before Death at Eight Weeks of Age.*

	Groups.		
	Spayed controls.	Progesterone (19–21 days).	Progesterone (19–21 days). Oestradiol (19–21 days).
Average daily absorption of progesterone	—	0·12 mg.	0·13 mg.
Average daily absorption of oestradiol	—	—	1·5 μg.
Nuclei per gland section . . .	11·0±0·90	12·4±0·78	7·2±0·51
Mitoses per 50 gland sections in 5 hours	13·8±2·55	11·0±1·09	12·2±1·98
Turnover time (days) . . .	11·2±1·98	12·5±1·22	7·5±1·28
Gland volume (μ^3)	178,900±29,600	202,200±20,100	100,640±12,700
Cell size (μ^3)	1,565±53	1,613±55	1,693±50
New cells per gland per day . .	12·6±2·14	11·1±1·44	9·7±2·06

Means and standard errors are for groups of 10 rats.

Spaying of rats 21 days before they were killed at 22 weeks of age caused a significant increase ($t = 2{\cdot}30$; $P < 0{\cdot}05$) in the size of the sebaceous glands (Table III) which appeared to be due to an increase in turnover time ; cell production was not affected. This result is in accordance with previous findings that oestradiol greatly decreases the size of the glands mainly by decreasing the turnover time of the cells (Ebling, 1948, 1954, 1955, 1957*a*). Progesterone had no significant effect on gland size, cell production or turnover time in intact rats. But in spayed rats progesterone appeared to reduce the size of the enlarged glands ($t = 2{\cdot}05$; $P = 0{\cdot}10 - 0{\cdot}05$) and it seems likely that this effect was due to a lowered rate of cell production, implying a lowered rate of secretion, rather than a change in turnover time.

TABLE III.—*Sebaceous Glands in Female Rats, Aged Twenty-two Weeks at Death.*

	Groups.			
	Intact.	Intact progesterone.	Spayed.	Spayed progesterone.
Average daily absorption of progesterone	—	0·16 mg.	—	0·18 mg.
Nuclei per gland section . .	10·3±0·49	9·8±0·35	12·1±0·60	10·3±0·62
Mitoses per 50 gland sections in 5 hours	22·2±3·06	19·5±2·65	20·6±3·13	15·7±1·51
Turnover time (days) . . .	5·6±0·76	6·0±0·65	7·6±1·20	7·6±1·12

Means and standard errors are for groups of 10 animals.

Mammary Glands.

The mammary glands of spayed 8-week-old rats were poorly developed, with a few thin straggly ducts. Rats treated with oestrogen and progesterone, however, had large branching glands bearing well-developed groups of alveoli in foliaceous lobules.

Discussion.

In these experiments, progesterone was not found to stimulate the sebaceous glands either in intact or in spayed, immature or mature female rats. Implantation of oestradiol for part or all of the period of progesterone treatment did not affect the sensitivity of the sebaceous glands to progesterone. Nevertheless, the dose of progesterone absorbed, which was of the order of 100–200 μg. per day for 21 days, in combination with oestradiol, caused marked alveolar development in the mammary glands.

Previously it has been shown that implants of testosterone, giving a similar rate of absorption of hormone, caused marked enlargement of the sebaceous glands, involving significant increases in cell size and in the incidence of mitoses, in both spayed female rats and castrated male rats (Ebling, 1957*a* and *b*). The current findings contradict those of Haskin *et al.* (1953) that progesterone has a stimulating effect on rat sebaceous glands, detectable even with a dose of 1 μg. per day for 30 days and comparable with that of testosterone when a massive dose (10 mg. per day) is used.

The evidence that progesterone does not stimulate the sebaceous glands of the rat is consonant with the finding of Jarrett (1959) that it does not increase sebum production in man and with his view that it is not involved in the aetiology of acne vulgaris.

I should like to thank Dr. W. J. Tindall of Organon Laboratories Ltd. for the implants of progesterone and oestradiol/cholesterol and Mr. John Skinner for technical help.

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EXPERIMENTS ON THE RELATIONSHIP BETWEEN THE NERVOUS SYSTEM AND HAIR GROWTH.*

L. BALUS.

Institute of Therapeutics, Sos. Stefan Cel Mare 89, Bucharest, Rumania.

The part played by the nervous system in the development of hair is still a problem concerning which available information is highly controversial, whether it concerns clinical observations or laboratory investigations in animals. Villaret (quoted in Desaux, 1953) observed changes in the hair in the cutaneous distribution of injured peripheral nerves. According to this author, hypertrichosis is met with in cases in which the injury of nerve structures is partial and curable, while conversely, when the lesion is total and re-establishment of nervous conduction out of the question, hypotrichosis is seen. Other authors have observed hypertrichosis in infantile paralysis, syringomyelia and spina bifida occulta. Numerous observations, such as hypertrichosis occurring during encephalitis or complete alopecia following lesions of the hypothalamus (Hoff, 1950), demonstrate the participation of the higher nerve centres in the development of hair. In dermatological practice, one of the more frequent affections of the hair is alopecia areata which frequently sets in after nervous shock or violent emotional disturbance and which is considered to be a neurovegetative dystonia (Lévy-Franckel, 1922 ; Romanenko, 1953). Tataru *et al.* (1956) reported a high rate of cure following the infiltration of bald patches with procaine. As regards the part played by the sympathetic system in hair development, Dargent (1941, quoted in Desaux, 1953) noticed considerable hypertrichosis following stellate ganglionectomy, occurring on the side operated upon. Piguet (1949) obtained good results in alopecia areata from procaine infiltration of the superior cervical ganglion. In contrast, some authors have contested the existence of any relationship between nerve lesions and disturbance of hair metabolism. According to them, hair is able to develop in the complete absence of nervous control. Flesch (1954) maintained that in man, division of sensory nerves and the sympathetic, or even total denervation, are of no consequence to the hair of the respective area.

Experimental findings reported in the literature are no less condradictory : Joseph (1886) induced areas of alopecia in cats by sectioning the occipital nerves. These results, however, were shown to be erroneous by Aubrun's (1932) control investigations. Saalfeld (1924) claimed to have obtained

*This work was carried out in the Department of Dermatology of the R.P.R. Academy, Director : Acad. St. Gh. Nicolau.

exaggerated hair growth in rabbits by cervical sympathectomy, but Cannon *et al.* (1929) showed that sympathectomy in cats did not influence the growth of hair. The absence of the nervous system does not appear to prevent the development of hair, as hair growth can be experimentally obtained in tissue cultures of the skin of monkey, rat and guinea-pig embryos.

Since the relationship between the nervous system and hair development is still obscure, an attempt was made to investigate this problem. Investigations had been directed for some time towards devising an experimental method of estimating the part played by the nervous system in cutaneous growth. The importance of the hair coat in the skin metabolism of various laboratory animals is well established. It is also well known that each hair follicle possesses an abundant nerve supply. An investigation of the morpho-physiological relationship between the hair follicle and the nervous system might thus possibly yield valuable information concerning the part played by nervous structures in the general growth of the skin.

In the first series of investigations an effort was made to establish whether the interruption of all nervous connections between the skin and the nerve centres caused any changes in the growth of hair. For this purpose hair growth in skin areas on the flanks of rabbits in which all nervous connections had been severed was compared with that in symmetrical control areas.

Methods.

In order to obtain a denervated skin area, recourse was had to Mansfeld's method (Pavlov, 1955). This is based upon the fact that in an area of the skin in which all connections with the adjacent tissues have been severed, nervous connections are not re-established for two to three months, while revascularization is completed during the first ten days following the operation. Thus it is possible to obtain for a period of about eight to ten weeks an area of skin in which every kind of nervous connection with the immediately adjacent nerve centres is sure to have been interrupted, while the other anatomical structures perform their normal functions.

In these experiments, male and female rabbits of various breeds were used, ranging from 2 to 2·5 kg. in body weight. The experiments were performed during the cold season in this country (December–March), the animals having previously been quarantined for several weeks. Denervation of a cutaneous area was carried out in two stages according to Mansfeld's technique. The first consisted of making a linear incision about 15 cm. long, parallel to the spine and at a distance of 1–2 cm. from it, penetrating down to the musculo-osseous layer. From one end of this incision, a second about 10 cm. long was then made at a right angle to the first and the skin area between the two incisions was separated from the underlying tissues by means of curved scissors, all nervous and vascular connections being carefully divided. The skin was again " mounted " in its place, by suturing the two incisions. After a period of 10 days, during which healing of the linear wounds was allowed to occur, the second stage of the operation was performed. This consisted of the same procedures as above, the incisions being made to delimit with the former ones a rectangular area measuring about 15 cm. long and 10 cm. wide. A skin area was thus obtained covering a large portion of the animal's flank, completely deprived of nervous connections for a period of at least two months. The latter fact was

confirmed by means of biopsies performed in the denervated area. By appropriate staining methods, the nerves in the dermis were found to display various degrees of degeneration. Moreover, when painful stimuli (pricking or pressure) were applied to the denervated area, no defence reflexes were elicited by the animal, while such reactions ensued when the stimuli were applied to the normal skin. Ten days after the second stage of the operation, the surface of the denervated area and an equivalent and symmetrical one on the opposite flank were epilated with barium sulphide paste. The growth of hair in the denervated and control areas was recorded daily. The experiments were performed in 22 rabbits, kept under observation for at least 3 months following the preparation of the denervated areas.

Results.

Hair growth set in sooner and progressed faster in the denervated skin than in the control area. In the denervated area, hair began to appear 3–6 days following epilation, while in the control area it appeared at the end of 8–9 days, sometimes even later. This resulted in the hair in the denervated area exceeding in length that of the control area by about 1 cm. $\pm$ 2–3 mm. in the period of the experiment. Sometimes the difference in length was so conspicuous that while the hair had reached its maximum length of about 3 cm. in the denervated area, equalling that of the immediately adjacent normal skin, not the least sign of growth could be noticed in the control area. About 4–5 weeks after epilation, when the hair on the denervated area measured 3–4 cm., growth came to an end. It had reached the same level as that on the surrounding normal skin, the area operated upon being hardly discernible. The same phenomena were seen on the control area, where, however, the process was delayed by 15–20 days compared with the denervated area. In most instances, at the end of about two months following denervation, the two areas became identical.

In some of the 22 rabbits, epilation was repeated in the same areas after two months had elapsed. The growth rate of the hair was again followed for another 3–4 weeks. Apart from barely perceptible variations, hair growth in the formerly denervated area now occurred at the same rate as in the control area. The shape, thickness and pigmentation did not vary during the experiment.

It is worth mentioning how the hair made its appearance. On the surface of the respective areas, patches of a bluish tint appeared here and there. In the course of 24–48 hours, these patches became more intensely coloured, almost black. After about another 3 days, sometimes a little later, the tips of the hairs appeared at the surface of these patches. As hair growth progressed, tufts of extremely variable shape and extent were formed, corresponding exactly to the bluish patches. This pattern of hair growth in tufts is due to the unequal cyclical development of the hair in different areas of the skin, which occurs in some fur-bearing animals including the rabbit.

Summing up this first series of experiments, in a skin area on the flank of a

rabbit denervated according to Mansfeld's method, hair was found to continue growing and grew faster than in a symmetrically situated area of normal skin in the same rabbit, during the two months following the operation, i.e. during the period in which the effects of the latter persisted. After two months, when the denervated skin area had recovered its nervous responsiveness, a difference could no longer be noticed between the rates of growth in the two cutaneous areas.

An attempt was made to devise in man an experiment comparable to that performed in rabbits, in order to verify and support the results obtained. For this purpose, the fate of hair in skin which had been grafted for plastic purposes was investigated during the months following the operation, i.e. in the period when the nerves had not yet regenerated. The denervated area created in rabbits was nothing more than a non-transplanted autologous graft, in every respect corresponding to grafted skin used in plastic operations in man. This anatomical and functional similarity between our experimental model and human grafts is confirmed by numerous investigations. Thus, Sazontov (1953) investigated the function of the sensory receptors in a great number of cutaneous grafts and found all types of response were abolished during the early months following operation and biopsies revealed the presence of degenerated nerve fibres. Recovery of all types of sensibility did not occur sooner than after 3–4 years. In these patients, plethysmographic tests disclosed that nervous control of vascular reactions was not regained for a period of about 3 years.

Starting from these considerations, 6 patients were investigated in whom skin grafts had been performed 2–7 months previously. In none of these cases was cutaneous responsiveness found to have returned. Small soft hairs of the "down" type, characteristic of the skin area from which the grafts had been taken, were present in five cases. The hairs were shaved. After about two weeks, the hairs had grown again reaching their former length of a few millimetres. In the sixth patient, the graft had been taken from the abdomen (linea alba), where the hairs had a length of about 1–1·5 cm. It was grafted on to the left thumb and was displayed marked hypertrichosis 4 months after the operation, the hairs exceeding 3 cm. in length.

From the results obtained in rabbits and man, the following conclusions may be drawn.

The germinative zone of the hair follicle is able to maintain its activity in the absence of cutaneous nerves.

In spite of the absence of nervous control, hair not only continues to grow, but growth progresses at an even greater rate in a denervated skin area. It follows that the nervous system, although it does not directly control the metabolism of hair, nevertheless plays some part in the dynamics of hair growth, by exerting an inhibiting action on hair-forming processes.

The main feature of the first experiment was the complete interruption of every nervous connection between the skin and the rest of the body. It is consequently impossible to state which of the nerve structures in particular, the vegetative or the somatic, were involved in the phenomena observed. A second experiment was therefore undertaken in order to establish what part the sympathetic system played in the development of hair. As mentioned above, the literature concerning this problem is scanty and contradictory.

Methods.

The anatomical sympathetic innervation of the rabbit's ear being supplied by the cervical sympathetic chain, resection of the latter was performed. The animals were anaesthetized (2–3 ml. of a 20% chloral hydrate solution per kg. body weight, by subcutaneous injection) and about 1 cm. of the cervical sympathetic chain situated near the bifurcation of the carotid artery was excised. The nerve loop crossing the anterior aspect of the artery was divided at the same time. The operation of sympathetic resection in the rabbt is easy to perform and causes very little trauma. The unilateral interruption of the sympathetic was tested by recording the local temperature of the rabbit's ears at the base and tip by means of a sensitive thermo-couple, before and after the operation.

Twenty-four hours after the performance of sympathectomy, both ears of the rabbit as well as the neighbouring cutaneous areas over a distance of 2–3 cm. were epilated by means of barium sulphide paste. The rate of hair growth was then recorded daily in the sympathectomized and symmetrically situated control areas. The area of most active growth, affording satisfactory conditions for observation, was situated in the lower third of the ear and around its root. On the other parts of the ear, the hair displayed a low degree of vitality expressed by its slow growth and relative sparsity. At first, experiments were performed in rabbits of various breeds. After several trials, rabbits possessing a uniform black coat were found to yield the best and most constant results. In order to follow hair growth more easily, we attempted to stimulate it in all the experimental animals. For this purpose each of the rabbits was given a total of 5–6 vials of 200,000 units of vitamin D_2 by intramuscular injection or orally, before and about 2 weeks after the operation. This vitamin appears to exert a stimulating action on hair growth.

Results.

Comparison of the rates of hair growth on the ears of 26 rabbits disclosed that in 22 hair developed more rapidly in the skin area on the sympathectomized side. Hair began to grow far sooner than in the normal skin, the difference ranging from a few days to 1–2 months; in most of the rabbits it was 7–10 days. This interval was expressed by the difference in length of the hair in the two areas under consideration, varying from 0·5 to 1 cm. Sometimes, however, this difference was very conspicuous, the hair on the sympathectomized ear having nearly completed its growth when on the control ear the first tufts had hardly appeared. After 4–6 weeks, hair growth had come to an end in the sympathectomized area, the fur being in no way different in its appearance before the operation. At the end of another 1–2 weeks the hair on both ears

was identical. However, in some rabbits, the difference in length of the hair to the advantage of the denervated area was maintained even 2–3 months after sympathectomy. In some of the animals, hair development progressed at the same rate in both areas for an initial period. However, after another week, hair growth on the sympathectomized side began to surpass that in the control area, the hair in the former area soon considerably exceeding in length that in the latter. As in the first experiment, the hair did not grow uniformly, but in tufts of various shapes and sizes. It was often preceded by brownish-blue spots which formed on the skin and from which the hair tips emerged a few days later. Eventually the hair tufts of various shapes coalesced and the former hairy surface was restored.

In six rabbits, a second epilation was performed after the hair had reached the same length on both areas. In four of these, the difference of growth rate persisted, the hair on the sympathectomized area again developing more rapidly than that on the symmetrical control area. In the other two rabbits, no difference in the length of hair on the two areas was noticed. The epilation was repeated after four months in the four rabbits which had maintained a difference in the growth rates of the hair. Only two of these continued to display changes in the rate of hair development : in these two, the differences were maintained for eight months in one and for nearly a year in the other which died at the end of that period.

As mentioned above, 4 of the 26 rabbits displayed no differences in the rate of growth. These latter results do not invalidate the findings made in the majority of the animals. Two of the four rabbits displayed the same growth rate in both areas. In the other two, the hair grew more rapidly on the control area than on the denervated, but the animals died 5–6 weeks after the performance of sympathectomy. Had it been possible to follow these animals for a longer period, they might possibly have furnished data confirming the results obtained in the majority under investigation.

Discussion.

The results of the first experiment showed that the nervous system in the normal skin inhibited hair development. The length of the hair was thus kept within physiological limits. The fact that interruption of the cervical sympathetic chain in rabbits resulted in more rapid development of the hair on the ear on the operated side than in the symmetrically situated control area, proved this inhibiting action on hair matrix to be exerted by the sympathetic

The question arises as to how the more rapid hair growth following sympathectomy in the rabbit might be explained. Is it exclusively due to cutaneous vasodilatation consequent upon the abolition of the physiological vasoconstricting effect of the sympathetic, or do the sympathetic fibres supplying the hair

follicle or terminating freely at various levels of the dermis exert a direct trophic action?

Comparative temperature recordings in the ears of the sympathectomized rabbits showed that the temperature on the side operated upon exceeded that of the other side by 1–3° C. The skin of the former area was thus a site of more active blood supply which may have accounted *per se* for the greater growth rate of the hairs. However, I do not consider this explanation to be entirely satisfactory for the following reasons.

The temperature differences mentioned decreased considerably after 15–20 days following the operation and in some animals even disappeared altogether. Moreover, repeated temperature recordings performed in several rabbits at short intervals (1, 2, 3 hours) on the skin of both ears before and after sympathectomy, disclosed variations of several degrees. These observations revealed the existence of a local vascular lability which was displayed in response to the most varied factors (change of room, head movements, season etc.), a phenomenon which tends to lessen the importance of vasodilatation as a permanent stimulus for hair growth.

Paralytic vasodilatation consequent on sympathectomy is known to be transitory, a compensating process due to an increased tonus of the smooth muscle of the vessels setting in after a period.

The differences in rate of growth of hair persisted for several months in some of the animals as shown above, while temperature differences between the two ears could no longer be recorded by that time.

During the phases of hair growth, the whole skin undergoes important changes. Thus, Borodach and Montagna (1956) have shown that the subcutaneous fat layer in young mice diminishes to half its initial thickness during the period of hair growth. These investigations have been confirmed by Andreasen. Likewise, Chase *et al.* found the epidermis to be acanthotic at the beginning of the cycle of hair development in rats and to become considerably thinner during the subsequent period. The sebaceous gland of the hair follicle undergoes similar quantitive changes.

By performing unilateral sympathectomy, the process of hair growth was activated in one of the rabbit's ears, i.e. a cycle of hair growth was determined by artificial means in every respect similar to the one observed under physiological circumstances. The same applies to the denervated flap created on the rabbit's flank.

Under these circumstances it is difficult to admit that all the metabolic changes which accompany the development of the fur in various laboratory animals including the rabbit should exclusively be due to more or less permanent vasodilatation.

Another question is whether the growth changes observed after sympathectomy are due to trophic nerve endings proper to the hair follicle. Various

authors have described the presence of numerous intra- and perifollicular nerve endings. It is nevertheless difficult to answer the above question because the sympathetic nature of these fibres has never been demonstrated. Moreover, hair growth has been shown to take place without any nervous participation: hairs grow in tissue cultures, hairs transplanted from one area to another maintain their viability and the experiment with the denervated flaps clearly demonstrated the growth of hair in the total absence of functioning nerve elements.

A further qualification must be made, viz., for what period is the hair follicle able to continue its activity *in vivo* in the absence of nervous control? In the above experiments, the activity of the nervous system was interrupted for a period of only a few months. In order to ascertain the part played by the nerve endings of the skin in hair growth under conditions of an irreversible suppression of their function, further investigations are required.

Thus, at the present state of knowledge, we cannot speak of the existence of sympathetic nerve endings pertaining to the hair follicle, the activity of which could account for the more rapid hair growth observed in the rabbit after cervical sympathectomy. As shown above, cutaneous vasodilatation cannot be the sole basis of hair development in these experimental conditions.

There seems no alternative to admitting that the different growth rates of the hair are due to nerve endings of the sympathetic system present at various levels in the dermis. Hair growth in fur-bearing animals involves a whole set of metabolic changes characterizing a cyclical process of pilogenetic activity. In pursuing this line of thought, the sympathetic nerve endings might be considered to be responsible for the whole of the cutaneous changes occurring during the hair cycle. In normal skin they act by inhibiting the growth of the hair follicle.

Finally, the results of these experiments suggest that the latter constitute useful tests of the part played by the sympathetic system in the growth of the skin as a whole.

Summary.

The author has experimentally investigated the relationship between hair growth and the nervous system in rabbits.

The method consisted of following the rate of hair growth in a skin area either denervated or subjected to distant sympathectomy, as compared with a symmetrical control area of normal skin in the same animal.

The hair in denervated cutaneous areas and on those corresponding to the sympathectomy grew more rapidly than the hair on the control area. This proves that the nervous system plays an inhibiting role, slowing down the activity of the hair matrix. This is exerted by the sympathetic system through its general trophic activity in the skin.

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BOOK REVIEWS.

The Skin and Mammary Gland*

This is a supplement to the third volume of von Möllendorff's *Handbuch der mikroscopischen Anatomie des Menschen.* It is difficult to discuss a work of this magnitude in a short review as even a longer analysis could assess only a fraction of the wealth of material presented. As one expects from a handbook, every aspect of the subjects is dealt with in a most thorough and distinct manner. The reader will find here information on the embryology, anatomy, histology, physiology, biochemistry and enzymology of the skin and mammary gland. The clear, excellently printed and illustrated text is supplemented by comprehensive bibliographies. This work should be available in all large dermatological teaching centres. In view of the high cost of such publication, it is a pity that the section dealing with the skin does not appear to be available as a separate volume. H. H.

The Apocrines.†

The rapid expansion in medical and scientific research over the past fifteen years is reflected in the alarming number of new journals which now appear each year. Even with library bulletins it is becoming increasingly difficult to keep pace with contributions in one's own limited sphere. Hence the growth of review papers, journals, and books. They serve a real need, particularly for newcomers to a particular field. This excellent monograph is one of the American Lecture Series in Dermatology published under the editorship of Dr. Arthur C. Curtis. They give a first-class account of the anatomy, physiology, pharmacology, and disorders of the apocrine gland, as well as what is known of the nature of apocrine sweat. The notable contributions of the authors and their collaborators are well known to dermatologists ; this description of their carefully designed and well executed experiments represents dermatological investigation at its very best. While acknowledging their research ability, one must also admire the wonderful facilities provided for them at the University of Pennsylvania, for which the authors pay tribute to Dr. D. M. Pillsbury and Dr. H. Beerman. Few departments can have ten, twenty, or ninety adult Negro subjects for continuous study involving sweat collection from individual glands, injections of stimulants, occlusion of duct orifices and biopsies. The authors have fully justified the facilities afforded them by extracting the maximum possible information. The direct observation of myoepithelial contractions and the work on chromidrosis are outstanding pieces of research in dermatology. This monograph should be in the possession of every dermatologist and should be compulsory reading for every student of dermatology as representing a model of research work. C. D. C.

**Die Haut.* E. Horstmann. *Die Milchdrüse.* A. Dabelow (1957). Berlin : Springer. Pp. 524, 359 illus. Price DM 198.

† *The Human Apocrine Sweat Gland in Health and Disease.* Harry J. Hurley and Walter B. Shelley. Springfield, Illinois : Charles C. Thomas. (1960.) Pp. 138. Price £3.

CURRENT LITERATURE.

ACUTE DISSEMINATED LUPUS ERYTHEMATOSUS, A COLLAGEN DISEASE AND A DISEASE OF AUTO-SENSITIZATION. R. Robineaux and G. Voisin. (1959) *Arch. belg. Derm. Syph.*, **15**, 371.

There is a definite connection between certain effects of the anaphylactic type of hypersensitization and collagen diseases, but although in anaphylaxis, periarteritis nodosa and acute rheumatism an exogenous antigen can be found to explain the phenomena, none can be found to explain the symptoms of systemic lupus erythematosus. It is argued that in systemic lupus erythematosus the antigen is situated in the cellular nuclei which become slightly modified under a bacterial, viral or toxic attack. J. K.

A CLINICAL AND GENETIC STUDY OF HEREDITARY PAPULAR KERATOSIS OF PALMS AND SOLES. E. Heierli-Forrer. (1959) *Dermatologica, Basel*, **119**, 309.

The author examined personally 62 relatives of her propositus, and found 15 examples of the condition, although the patient had been shown in 1955 as an isolated case. She emphasizes the necessity for personal examination in all genetic studies, and reports two positive findings in persons who had given a negative reply to a written question. She concludes that keratodermia maculosa disseminata symmetrica palmaris et plantaris (Buschke-Fisher), and keratoma dissipatum hereditarium palmare et plantare (Brauer) are identical, but that porokeratose papillomateuse palmaire et plantaire (Mantoux) is different. J. F. S.

DISSEMINATED JUVENILE XANTHOMA-LENTIGO WITH DIABETES INSIPIDUS AND HYPERLIPIDAEMIA. B. Duperrat, Nguyen Van Ut and Nguyen The Huy. (1959) *Dermatologica, Basel*, **119**, 328.

A 16-year-old Vietnamese boy showed a profuse eruption of deeply-pigmented spots, indistinguishable clinically from lentigines, starting on the eyelids some two years previously, and now most numerous in the flexures and round the orifices. Histologically, they showed typical foam-cells in foci in the corium, and abnormally numerous melanoblasts in the basal layer of the epidermis. The melanoblastic activity was greatest immediately over the xanthomatous foci, and recalled that seen in junction naevi. His serum contained total cholesterol 1·15 per mille, esterised cholesterol 0·70, total lipids 11·50. His mother, the only relative available for examination, had serum lipids 11·30 per mille, and 0·420 phospholipids—extraordinary figures for a Vietnamese peasant, whose staple diet is rice. J. F. S.

SCLERODERMA WITH BULLOUS LESIONS. John Garb and Charles F. Sims. (1959) *Dermatologica, Basel*, **119**, 341.

The formation of bullae in scleroderma is rare, but this case is apparently the 25th so far in the literature. The first was recorded by Leisrink as far back as 1869. Lichen sclerosus et atrophicus must obviously be excluded in making the diagnosis, and the authors consider that most, if not all of the published cases satisfy this condition. Their patient, a woman aged 70, reported in 1953 with banal scleroderma, worst on her abdomen. In June 1954, some ulceration was noted, and in November 1954, definite blisters were observed on sclerodermatous patches on her abdomen. Blisters continued to appear for several years, but by June, 1958, the condition had subsided, leaving extensive atrophic areas, but no rigidity. The main treatment was with chloroquine, but the authors think that a natural " burning-out " of the disease was the likeliest cause of the good result. J. F. S.

ADJUVANTS IN THE RUBBER INDUSTRY AS CAUSES OF DERMATITIS. W. P. Herrmann and K. H. Schulz. (1960) *Dermatologica, Basel.*, **120**, 127.

Between 1953 and 1958, 8000 patients with contact dermatitis have been seen (in Hamburg-Eppendorf), and in 63 the dermatitis was due to rubber. Of these, 29 were occupational, 16 being in the rubber industry. The commonest causative agents found were 2-mercaptobenzothiazol and tetramethylthiuram disulphide. During the same period 13 patients were seen whose

dermatitis was caused by dress-protectors, the most usual cause in these cases being 4,4-dioxydiphenyl. With the help of tests done with 15 substances used as accelerators, and to prevent ageing of the rubber, it was shown that derivatives of thiourea could cause cross-sensitizations. Apart from the manufacture of rubber, some of these substances, known to be sensitizers, are used in other forms of occupation. It is of practical importance to know where such substances are used. (Slightly modified from Authors' abstract.) J. F. S.

SKIN CHANGES AFTER THE THERAPEUTIC ADMINISTRATION OF LARGE DOSES OF NICOTINIC ACID. M. Ruiter and L. Meyler. (1960) *Dermatologica, Basel*, **120**, 139.

In a 42-year-old man with hypercholesteraemia, who was treated with 3 g. daily of nicotinic acid, as recommended by Parsons *et al.*, extensive skin changes were noted, especially on his trunk and extremities. The skin was dry, rough, slightly scaly and looked reticulated. The colour was a dirty grey, and in the worst areas greyish-brown. Especially in the latter areas (i.e., round the axillary folds, at the lower part of the back, in the inguinal region and at the upper part of the abdomen and loins) the skin looked granular. At the same time patches of depigmentation were seen. Histologically, the horny layer was enormously thickened, but not parakeratotic, while the corium was normal. On cessation of treatment the skin manifestations vanished, only to reappear on resumption, and this happened several times. Similar though slighter changes were observed in three other patients on this treatment (the efficacy of which in reducing the blood-cholesterol is fully endorsed), and two of them had also rhagades at the oral commissures, and this yielded to the administration of vitamin B_1. This leads the authors to suggest that the massive doses of one vitamin upset the entire vitamin balance of the patients. J. F. S.

MULTICENTRIC LIPOMA-LIKE SCLEROSIS OF THE FATTY TISSUE FROM VENULAR THROMBOSIS. D. Held and R. Della Santa. (1960) *Dermatologica, Basel*, **120**, 145.

The authors, with another colleague, Rutishauser, have separated from the group of fibro-lipomata a peculiar entity, attributable to local vascular changes. Their series consisted of six men and one woman, aged 26–45. There have been no subjective symptoms, and all are seemingly in good general health. They describe in detail one illustrative case, in a man aged 37. Nodules come in the subcutaneous fat, spread and multiply. Histologically, they resemble fibro-lipomata, but they can be seen to be based on thrombotic obliteration of venous capillaries. The cause is unknown. J. F. S.

AN ATTEMPT AT THE CLASSIFICATION OF THE HEREDITARY PALMO-PLANTAR KERATOSES, WITH REFERENCE TO ASSOCIATED SYMPTOMS. A. Franceschetti and U. W. Schnyder. (1960) *Dermatologica, Basel*, **120**, 154.

Whereas keratosis palmo-plantaris having a dominant mode of inheritance usually occurs exclusively as localized hyperkeratoses of the palms, soles and neighbouring skin, keratosis palmo-plantaris with a recessive mode of inheritance is accompanied by other ectodermal anomalies. The law according to which dominant forms are generally less severe than recessive forms is confirmed in the case of keratosis palmo-plantaris, the recessive forms, in fact, being part of general disorder of the ectoderm. The authors show that a classification of keratosis palmo-plantaris hereditaria, derived from a study of the literature and from their own cases, must be based not only on the symptomatology but also on the genetic pattern. J. F. S.

FURTHER HISTOLOGICAL FINDINGS IN NODULAR PRURIGO OF HYDE. J. Gay Prieto, A. P. Rodriguez Perez and G. Jaqueti. (1959) *Act. derm-sifilogr., Madr.*, **50**, 19.

The histology was discussed further. Since nerve fibre changes could be found before the appearance of any inflammatory infiltrate, the nerve changes were considered the primary lesion. In one of their cases sections of skin from untreated and treated lesions, as well as skin near to and distant from the nodules, were examined. The hyperpigmentation was found to persist after clinical cure. The inflammatory infiltrate was universal around degenerated nerve fibres. These changes were quite easy to see in the skin clinically unaffected, as well as in nodules whether treated or untreated. The conclusion reached was that the disease was not local but that all the skin was involved, although why nodules developed at some sites only was unexplained. Mast cells, however, were almost absent from treated areas or areas of skin far away from clinical nodules. The hyperpigmentation and mast cells might relate the condition to urticaria pigmentosa. P. I.

MELANOSIS OF RIEHL OF EMOTIONAL ORIGIN. C. Aguilera Maruri. (1959) *Act. dermsifilogr., Madr.*, **50**, 23.

A woman aged 60 had had a widespread vitiligo from the age of 22. She was an emotional person and was wont to weep abundantly at any sort of upset. In February 1957 she was alone in the house when she opened the door to her brother who collapsed dead in her arms. The next night her face became red and swollen and intensely itchy. The redness lasted some days and was followed by a progressive darkening. Histological study of the darkened skin was confirmatory of melanosis of Riehl.

Although the author was in no doubt that the pigmentation was of pituitary origin, the type of pituitary cell responsible was considered uncertain. Arguments advanced in favour of the basophil cells were that generalized pigmentation was common in basophil adenoma. Pigmentation was also common in acromegaly, but in this condition basophil cells might also be increased. In chromophobe adenoma with the adipose genital syndrome pigmentation was very light. Although for the above reasons it might appear that the basophil cells were the source of the pigmentation, the author pointed out that melanotrophic hormone appeared during early embryonic life and before differentiation of the basal cells. P. I.

NEW HISTOCHEMICAL ASPECTS OF COLLOID MILIUM. A. P. Rodriguez Perez and G. Jaqueti del Pozo. (1959) *Act. derm-sifilogr., Madr.*, **50**, 233.

From morphological and histochemical studies of two cases of colloid milium the authors concluded that the origin of the material filling the vesicles depended on a complex series of factors. They found that disintegration products of elastic and collagen fibres were concerned. They also found interstitial mucopolysaccharides identifiable as β chondroitin sulphuric acid played a part, as well as products originating from the serum. P. I.

A CASE OF MULTIPLE CUTANEOUS OSTEOMAS. J. Mercadal Peyri. (1959) *Act. dermsifilogr., Madr*, **50**, 250.

A labourer aged 28 had multiple cutaneous osteomas confined to the legs. Fourteen years previously he had had a deep wound damaging the periosteum of the anterolateral part of the lower third of the left leg. Ten years previously he had sustained a similar wound on the anteromedial part of the same leg at a similar level. Since the first accident he had noticed the slow appearance and growth of multiple small tumours over the lower legs. The right leg was stated to have been subjected to multiple minor injuries and erosions, and one deeper wound due to the habitual wearing of sandals. On examination the middle and lower third of both legs were covered with hard nodules—about twelve on the right leg and some thirty on the left. Many lesions were the size of a millet seed or pinhead. They were generally pink or brown in colour; hard and covered by atrophic skin. A few were larger up to 3 or 4 mm. in diameter, and one was 2 cm. in diameter.

Microscopically the lesions were true bone with Haversian systems and fibro-fatty vascular medulla.

The injuries were considered responsible for the appearance of the tumours. P. I.

THE PUBLIC HEALTH STRUGGLE AGAINST BURNS. F. de Dulanto. (1959) *Act. dermsifilogr., Madr.*, **50**, 539.

Suggestions are drawn up for a national propaganda campaign to reduce the incidence of burns. Pamphlet distribution and special instructions in schools and religious colleges is advocated. The humbler type of Spanish dwelling in which there is a combined living room and kitchen is condemned as a source of accidents.

A plea is made for the formation of treatment centres for burns by pooling the resources of the Dermatological service with the Public Health and Blood Transfusion services. The proposed centres should have between 20 and 30 beds and two operating theatres, one clean and the other septic. There should also be skin banks and conservation of cadaver skin for this purpose. P. I.

FALL AND WHITENING OF HAIR. A. M. N. Zanon. (1959) *Act. derm-sifilogr., Madr.*, **50**, 543.

Hair colour depends on melanogenesis under the control of the middle lobe of the pituitary with its connections in the hypothalamus and the endocrine and neurovegetative systems. Hypo-

physectomy and anterior lobe pituitary adenomas produce hair atrophy, as well as do emotional shocks. The author surmises a faculty of the hypothalamic pituitary axis promoting permanence of the hair and regulated by central connections with gonadal influence.

Seborrhoeic alopecia is so called because it is preceded immediately by seborrhoea. Although seborrhoea and hair loss may be genetically identical the author believes that hair fall following seborrhoea is not produced only by the seborrhoea. P. I.

PRELIMINARY TRIAL OF TREATMENT OF RECURRENT HERPES WITH ANTI-POLIOMYELITIS VACCINE AND WITH LYSOZYME. S. Noguer-More, J. Borrell and S. Noguer Debray. (1960) *Act. derm-sifilogr., Madr.*, **61**, 25.

Nineteen cases of recurrent herpes with a minimum attack rate of 4 or 5 yearly were treated with anti-poliomyelitis vaccine. Three strains of virus which were completely inactivated but which retained antigenicity were used, the vaccine being supplied by Mme. Trefouel of the Pasteur Institute. Results were good in about a third of the cases treated.

Eleven cases were treated with lysozyme. The lysozyme was given as intramuscular injections daily for 8 to 10 days the dose being 37·5 to 75 mg. In 2 menstrual cases 30 mg. daily orally was also given in tablet form during the menses. Three had a remission of about a year with this treatment. P. I.

X-RAY THERAPY OF PALMAR AND PLANTAR HYPERIDROSIS. L. Azua. (1960) *Act. derm-sifilogr., Madr.*, **61**, 30.

Seven patients with palmar hyperidrosis, two of whom also had plantar hyperidrosis were treated. In four the factors were 90 KV and 2 mm.Al. and in three 110 KV. and 4 mm.Al. The F.S.D. was 30 cm. except for one case when it was 25 cm. and a single field of radiation for each palm or sole was used. The total dosage varied between 800 and 2594 r and the period of follow-up varied from two and a half months to ten years. In all except two cases the total dose was given in less than six months the individual treatment most often being 300 or 400 r at varying intervals.

Five cases are regarded as being completely and satisfactorily cured, one case was much improved and one case was a failure. No case showed evidence of radiodermatitis. The case receiving the largest dose of 2594 r, which the author thinks may have been excessive, has been at work for ten years since without abnormality of inconvenience. P. I.

SNEDDON AND WILKINSON'S SUBCORNEAL PUSTULAR DERMATOSIS. J. Gomez Orbaneja. (1960) *Act. derm-sifilogr., Madr.*, **61**, 1.

The author reports a typical case of the disease in a man aged 76 in whom five biopsies had shown subcorneal bullae. The vesicle fluid contained polymorphs the roof being formed by horny layer and the base by granular layer. In discussing the condition reference is made to a paper by Musimeci describing a case in which histological lesions of Duhring's disease and subcorneal pustular dermatosis co-existed. The author also refers to a case under observation in 1956 which clinically resembled Sneddon and Wilkinson's disease exactly but the blisters of which were subepidermal.

The cases of subcorneal dermatosis described are considered to be different from pustular psoriasis or acrodermatitis because the lesions of the latter involve the epidermis the lesions being subcorneal only in the former. Differentiation from Andrew's pustular bacterid is considered more difficult. Reference is made to Hellier's case in which pustular dermatosis followed a pustular eruption of the soles by some years. P. I.

ACRODERMATITIS ENTEROPATHICA. X. Vilanova, J. M. de Moragas and F. Prandi. (1960) *Act. derm-sifilogr., Madr.*, **61**, 12.

In a female child of six months, the skin lesions were characteristic of acrodermatitis enteropathica. A point is made that over areas subjected to trauma, and especially the heels, blisters as large as 5 cm. in diameter and full of tense serum occurred. The periorificial lesions and alopecia were usual. The child had had chronic diarrhoea since early infancy and the faeces were bulky, foamy and fatty with a microscopic appearance typical of steatorrhoea. She was treated by a gluten free diet and the chronic diarrhoea became much improved. Additional features were mild photophobia, apathy and marked anorexia. Growth was grossly retarded and the head was inclined forwards and to the left. Histologically some dyskeratosis with acantholysis and resemblance to *corps ronds* were seen as described by Piper. The bullae, however, were due to dermo epidermal separation. Dermal oedema was present with very marked changes in the papillary capillaries. These were dilated containing masses of red blood cells and intense endothelial

proliferation. The histological picture was considered diagnostic. In the comment, the onset of the condition at the change over from breast to bottle feeding is stressed and a digestive cause for the disease thought likely. Diiodohydroxy-quinolin did not control the illness satisfactorily. P. I.

IMMUNOLOGICAL ASPECTS OF LUPUS ERYTHEMATOSUS WITH PARTICULAR REFERENCE TO THE SYSTEMIC VARIETY. L. Rasponi. (1959) *Arch. ital. Derm.*, **29**, 137.

The author's own work and the experience of others confirm the view that in lupus erythematosus there is a complex and polyvalent formation of antibodies, particularly in the acute form of the disease. The antibodies are contained in the gamma globulin fraction and some of them can be classed as auto-antibodies. The conception of lupus erythematosus as an auto-antibody disease has much to recommend it. A. L.

THE EFFECT OF SOME HISTOLOGICAL STAINS ON THE BIREFRINGENCE OF THE HUMAN SKIN. A. Piredda. (1959) *Arch. ital. Derm.*, **29**, 201.

Some stains, particularly haematoxylin-safranin-orange, markedly increase the birefringence of the human skin. A. L.

INVESTIGATION OF LIPOPROTEIN METABOLISM IN DERMATOLOGY. I. NORMALS AND PSORIASIS. A. Longhi. (1959) *Arch. ital. Derm.*, **29**, 217.

There is a suggestion of slight enzyme disturbance in the lipoprotein metabolism of psoriasis as evidenced by a deficiency of the slow alpha fraction. A. L.

VARIATIONS IN THE SULPHYDRYL GROUPS IN THE SQUAMES OF PSORIASIS AFTER INJECTIONS OF B.A.L. L. Gigli. (1959) *Arch. ital. Derm.*, **29**, 268.

The quantity of SH groups in the squames varied widely from case to case and tended to be raised for the first 24 hours after an injection. A. L.

FURTHER RESEARCHES ON THE KIMMIG EFFECT. P. Moroni. (1959) *Arch. ital. Derm.*, **29**, 277.

Acid extracts of urine obtained from patients who have eruptions provoked by light often contain substances that produce absorption in the 480–520 Å region of the spectrum. The urine also has photodynamic properties when applied to the skin. There is often prophyrin present in the urine but this substance is not primarily responsible for the Kimmig effect, which is found mainly in polymorphic light eruptions, to a lesser extent in chronic lupus erythematosus and occasionally in other dermatoses. A. L.

INVESTIGATIONS ON THE DISTRIBUTION AND BEHAVIOUR OF ELECTROLYTES IN SKIN DISEASE. I. U. Silvestri. (1959) *Arch. ital. Derm.*, **29**, 317.

This article deals with the electrolytes in the blood, blister fluid and urine of burned patients. The serum potassium is raised early and may fail to return to the normal range even after complete healing of the skin. Serum sodium behaves irregularly and serum chloride is reduced, especially at first. The sodium and chloride content of the blister fluid parallels the blood level. The excretion of the ions in the urine varies a great deal and does not bear any obvious relation to their blood levels. The serum levels of calcium, magnesium, iron and copper were also investigated. A. L.

INVESTIGATIONS ON THE DISTRIBUTION AND BEHAVIOUR OF ELECTROLYTES IN SKIN DISEASE. II. U. Silvestri. (1959) *Arch. ital. Derm.*, **29**, 416.

This article deals with the spectrography of trace elements in the serum of burned patients. The significance of the presence of the trace elements demonstrated (silicon, titanium, silver, cobalt, nickel, bismuth, lithium, vanadium, chromium, strontium and barium) is doubtful. A. L.

THE EFFECT OF LYSOZYME ON THE REACTIVITY OF THE SKIN AND THE ABILITY OF SUBSTANCES TO DIFFUSE THROUGH IT. A. Zanca and M. Benatti. (1959) *Arch. ital. Derm.*, **29**, 341.

Lysozyme injected locally before doing a tuberculin test results in a reaction which is more diffuse but less indurated and less prolonged than that produced by tuberculin in untreated skin.

Hyaluronidase is reported to produce a similar effect. The injection of lysozyme mixed with trypan blue, however, usually results in the dye spreading less widely than does trypan blue mixed with saline, though in a minority (20%) of cases the spread with lysozyme is greater. Pemphigus vulgaris reacts in the latter fashion. A. L.

CUTANEOUS REACTIVITY TO STREPTOCOCCAL ANTITOXIN. G. Zavarini. (1959) *Arch. ital. Derm.*, **29**, 353.

All the subjects reacted to a dilution (in distilled water) of 1 in 25 and none to a dilution of 1 in 5000, and in between these limits there was an S-shaped curve of diminishing reactivity. It was not possible to correlate the vigour of the reaction with the clinical features of the case. A. L.

THE OCCURRENCE OF PROTEIN INCLUSIONS WITHIN LEUCOCYTES IN CRYOGLOBULINAEMIA. L. Rasponi. (1959) *Arch. ital. Derm.*, **29**, 379.

Inclusion bodies consisting of cryoglobulin could be demonstrated in some cases of both the primary and the symptomatic forms of the syndrome. The inclusions differ from the L.E. cell phenomenon which, however, may be present in the same blood sample. A. L.

PSYCHIC FACTORS IN PRURITUS VULVAE. L. Gigli. (1959) *Arch. ital. Derm.*, **29**, 392.

Sexual frigidity is the basis of most cases. Patience, humanity and understanding should be the watchwords of the patient's physician. A. L.

UNUSUAL IMMUNOLOGICAL FINDINGS IN A CASE OF CIRCUMSCRIBED SCLERODERMA. L. Rasponi. (1959) *Arch. ital. Derm.*, **29**, 406.

The case, which presented similar immunological perculiarities to those encountered in disseminated lupus erythematosus including the presence of L.E. cells, is said to have been one of localized scleroderma. The clinical features reported are very sketchy but it is clear that the sclerodermatous changes were widespread, that the muscles were involved and that the patient was an adolescent girl. A. L.

THE INFLUENCE OF ANOXAEMIA ON THE ACTION OF VISIBLE AND LONG ULTRA-VIOLET RADIATIONS ON THE GROUND SUBSTANCE OF THE SKIN. P. Moroni. (1959) *Arch. ital. Derm.*, **29**, 441.

The diffusion of haemoglobin in irradiated skin is lessened by anoxaemia. In light eruptions and lupus erythematosus the diffusion of haemoglobin in irradiated skin is greater than normal and the effect of anoxaemia is again inhibitory. A. L.

THE EXCRETION OF CHLOROQUINE IN SKIN PATIENTS. A. Zanca and M. Benatti. (1959) *Arch. ital. Derm.*, **29**, 462.

Using a method described by Haskins (1958) *Amer. J. trop. Med.*, **2**, 199, the authors found that the excretion of chloroquine in the urine was slow, discontinuous, not given to regular diurnal variation, had no connection with its therapeutic efficiency and was not interfered with by other drugs. A. L.

THE ISOLATION OF A SPECIFIC PATHOGENIC VIRUS FROM DISEASES OF THE PEMPHIGUS GROUP. A. Crosti, F. Gianotti and E. Hahn. (1959) *G. ital. Derm., Sif.* **100**, 229.

A filterable agent was isolated from the skin, mucous membranes, blood, C.S.F., and blister fluid—but not the saliva—of patients suffering from major blistering eruptions such as pemphigus, dermatitis herpetiformis, pemphigoid, erythema multiforme bullosum, Stevens-Johnson syndrome and pemphigus neonatorum (1 case), but not from epidermolysis bullosa (1 case). The agent, which was detected by its cytotoxic effect on a culture of human epithelial tissue (KB strain), could be passed, was titratable, and was visible under the electron microscope as roundish bodies between 20 and 30 μ in diameter. No neutralization could be demonstrated with hyperimmune sera from herpes, poliomyelitis or lymphogranuloma inguinale. Filtered material from a patient with pemphigus injected into the brain of a rabbit killed the animal and the virus was recoverable from the rabbit's tissues. A. L.

DERMATOLOGICAL PROBLEMS OF ADOLESCENCE. J. T. Ingram. (1960) *Practitioner*, **184**, 308.

Endocrine and psychological changes occurring in adolescents reflect on the skin with increased activity and size of the sebaceous glands. The " seborrhoeic " changes may be responsible for a wide range of dermatoses including pityriasis corporis, acne vulgaris, pyoderma, especially follicular lesions such as pustules and boils, and inflammation of the eczematous type.

Treatment of these conditions is discussed, in addition to that of psoriasis, ringworm, warts, alopecia and hirsutes. R. J. C.

HYPERKERATOSIS OF THE PALMS. H. R. Vickers. (1960) *Practitioner*, **184**, 350.

A useful discussion on the differential diagnosis and treatment of hyperkeratosis of the palms. R. J. C.

PENICILLINASE TREATMENT OF PENICILLIN REACTIONS. R. M. Becker. (1960) *Practitioner*, **184**, 447.

Penicillinase hydrolyses penicillin both *in vitro* and *in vivo*. Clinical trials have shown that penicillin could not be demonstrated in the circulation thirty to sixty minutes after a subcutaneous injection of penicillinase. Eight cases of penicillin sensitivity reactions that responded well to penicillinase are reported. In one with acute renal shutdown that had failed to respond to corticotrophin, steroids and antihistamines, there was marked diuresis within four hours of an injection of penicillinase. In a series of 53 cases several patients complained of pain at the site of injections, which usually subsided within twenty-four hours, and there have been occasional systemic reactions to penicillinase. In penicillin sensitivity reactions the earlier penicillinase is given the more rapid and complete will be the response. R. J. C.

THE USE AND ABUSE OF DETERGENTS. E. Waddington. (1960) *Practitioner*, **184**, 532.

Synthetic detergents are mild primary irritants and only rarely sensitizers. Skin damage may result from prolonged exposure to excessively hot or concentrated solutions, failure to rinse and dry the hands and failure to protect the hands. The clinical features and management are discussed.

Detergents have been incorporated in ointment bases, hair shampoos and antiseptics with advantage and are useful in seborrhoeic conditions. R. J. C.

GRISEOFULVIN. D. I. Williams. (1960) *Practitioner*, **184**, 383.

A very full account of the history, chemistry, pharmacology and toxicology of griseofulvin. Side-effects and indications for the use of griseofulvin in various fungal infections are reviewed. The dose recommended is 1 g. daily and in ringworm of the nails therapy may be required for six months. R. J. C.

THE PROBLEM OF PSORIASIS. E. J. Moynahan. (1960) *Practitioner*, **184**, 557.

A review of the incidence, genetic and racial factors and the biochemical abnormalities found in psoriasis. There appears to be a deficiency in the dipeptidase activity in the psoriatic skin and further biochemical studies may help to elicit this disorder of keratinization. Topical and systemic therapy is discussed. R. J. C.

LICHEN PLANUS. P. D. Samman. (1960) *Practitioner*, **184**, 564.

Papular hypertrophy, annular lesions, follicular atrophy, lesions of the mucous membranes and nail changes are described. The microscopy is characteristic. The average duration of the disease is eighteen months.

Steroid treatment benefits severe cases, but probably does not alter the duration of the disease. Rest, sedatives and topical applications are useful in all other cases. R. J. C.

THE NEURODERMATOSES. R. D. Sweet. (1960) *Practitioner*, **184**, 572.

Eruptions associated with stress and anxiety include chronic urticaria, eczematous neurodermatoses, atopic eczema, lichen simplex and anogenital pruritus.

Treatment consists chiefly of rest and reassurance. Sedatives, topical applications of hydrocortisone to begin with and other soothing medicaments are useful. Only in a few cases are systemic steroids indicated. R. J. C.

DISORDERS OF PIGMENTATION. E. W. Prosser Thomas. (1960) *Practitioner*, **184**, 582.

The depth of colour of the skin is due to more than one gene and in darker races there are additional genes, the darker pigmentation being dominant to lighter. Inherited and developmental abnormalities include albinism and incontinentia pigmenti. Freckles have a strong hereditary basis and lentigines, which appear earlier in life than freckles, are present in almost everyone. Endocrine and metabolic causes of pigmentation include Addison's disease, chloasma of pregnancy and cachectic states. Acanthosis nigricans and the Peutz-Jeghers syndrome illustrate how cutaneous manifestations can lead to the diagnosis of internal disease. Photosensitivity melanodermas, vitiligo, toxic melanoses, metallic pigmentation and carotinoid pigmentation are also discussed. R. J. C.

CONGENITAL AFFECTIONS OF THE SKIN. B. Solomons. (1960) *Practitioner*, **184**, 596.

An interesting discussion on some of the congenital skin diseases including ichthyosis, congenital ichthyosiform erythroderma, tylosis palmaris et plantaris, haemangiomas, epidermolysis bullosa and neurofibromatosis. R. J. C.

CORTICOSTEROIDS IN DERMATOLOGY. C. D. Calnan. (1960) *Practitioner*, **184**, 605.

Systemic corticosteroids are indicated in three main groups of patients : (i) Those whose life is, or may be, in danger : acute systemic lupus erythematosus, erythrodermia, pemphigus and pemphigoid, acute drug reactions of severe degree, the Stevens-Johnson type of erythema multiforme and anaphylactoid purpura. (ii) Those with severe acute dermatoses expected to be of short duration : acute lichen planus, contact dermatitis and drug reactions. (iii) Those with benign chronic disabling disorders : widespread eczema and exfoliative dermatitis, severe alopecia areata, psoriasis, cutaneous reticuloses and sarcoidosis. The choice of preparations, dosage and side-effects are described.

Topical therapy can only be reliably recommended for eczema or dermatitis, ano-genital pruritus, and perhaps facial and flexural psoriasis. Fine suspensions of hydrocortisone can be effective when injected locally into cutaneous lesions and this method has been used in alopecia areata, necrobiosis lipoidica, granuloma annulare, sarcoidosis, discoid lupus erythematosus and several other conditions. R. J. C.

OCCUPATIONAL DERMATITIS. S. T. Anning. (1960) *Practitioner*, **184**, 612.

Occupational eczematous dermatitis may result from either primary irritants or cutaneous sensitizers. On occasion there may be provocation of a constitutional endogenous eczema by working conditions. The diagnosis rests often on a detailed and careful history and thorough examination. Interesting examples of occupational dermatitis are given and the value of patch testing is mentioned. R. J. C.

ALOPECIA MUCINOSA WITH EOSINOPHIL GRANULOMA, LICHEN SPINULOSUS AND CHANCRIFORM LESIONS. G. H. Findlay and L. J. A. Loewenthal. (1960) *Dermatologica, Basel*, **120**, 263.

Six cases are described, bringing the total published to 30. The authors draw certain tentative conclusions :

(i) Alopecia mucinosa has features of premycosis and mycosis fungoides, without so far as we know developing the irreversible changes expected in those conditions. It appears therefore as if it were not a follicular symptom of mycosis fungoides or eosinophilic granuloma, as Braun-Falco assumes, but potentially a reticulo-granuloma in its own right, with a benign course, despite occasional ulcerations.

(ii) As with other histiocytoses and reticuloses of a more malignant type, it may be associated with many " non-specific " eczematoid changes, whose histological features are reported here, and which show little to suggest alopecia mucinosa in its typical form.

(iii) The clinical alopecia may be minimal in cases where at present no diagnosis other than a.m. is possible.

(iv) A non-specific adenopathy is described.

(v) The follicular " phthisis " of the disease seems not to be accompanied by a sufficiently constant or easily demonstrable increase in mucin to make this feature an essential requirement for the diagnosis. J. F. S.